Transactions of the Sixty-seventh Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Va., Sept. 6-8, 1956

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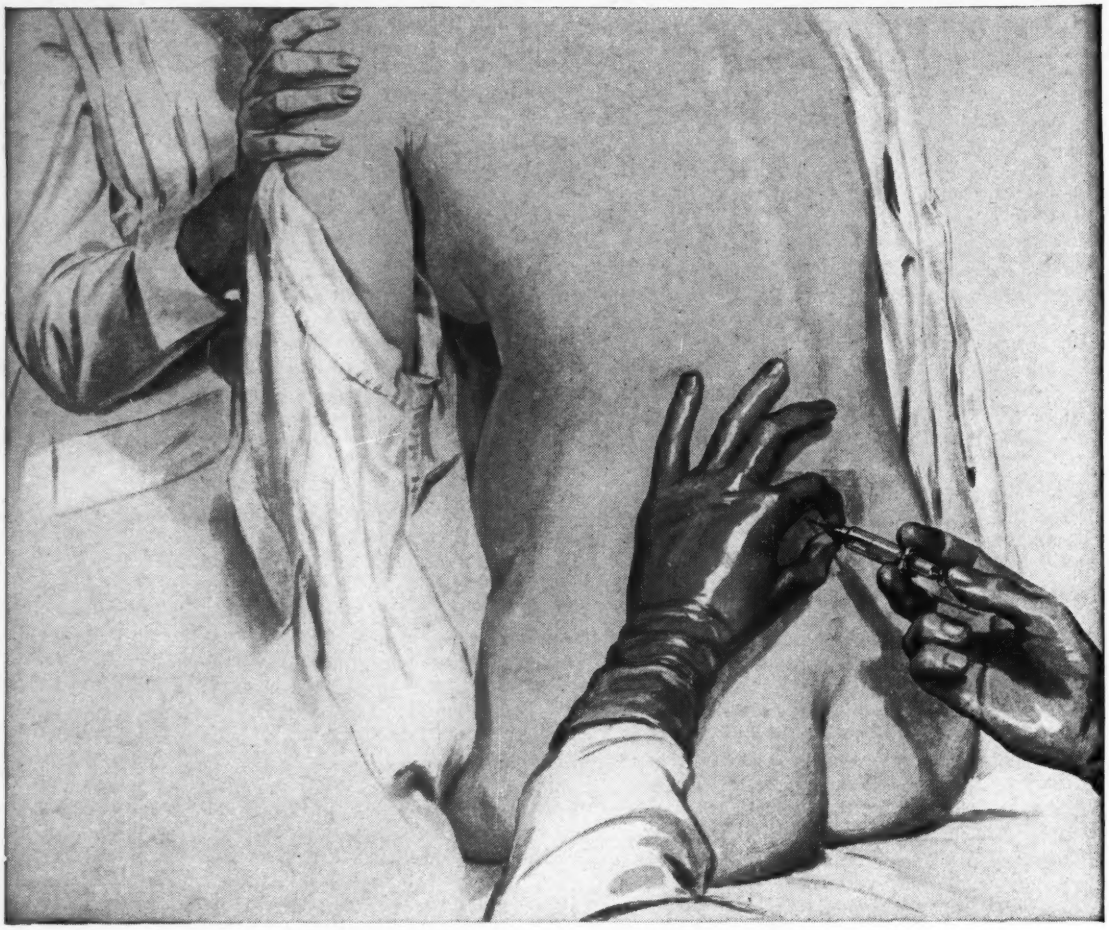

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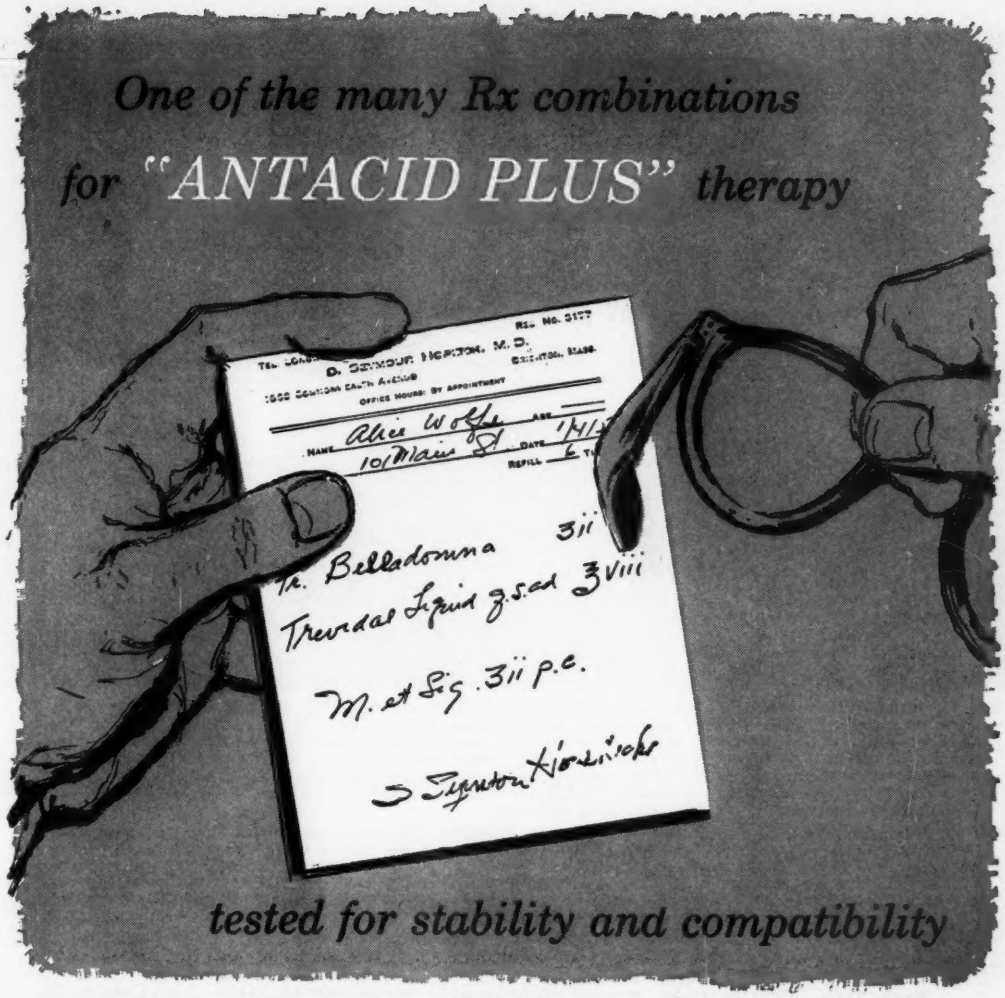

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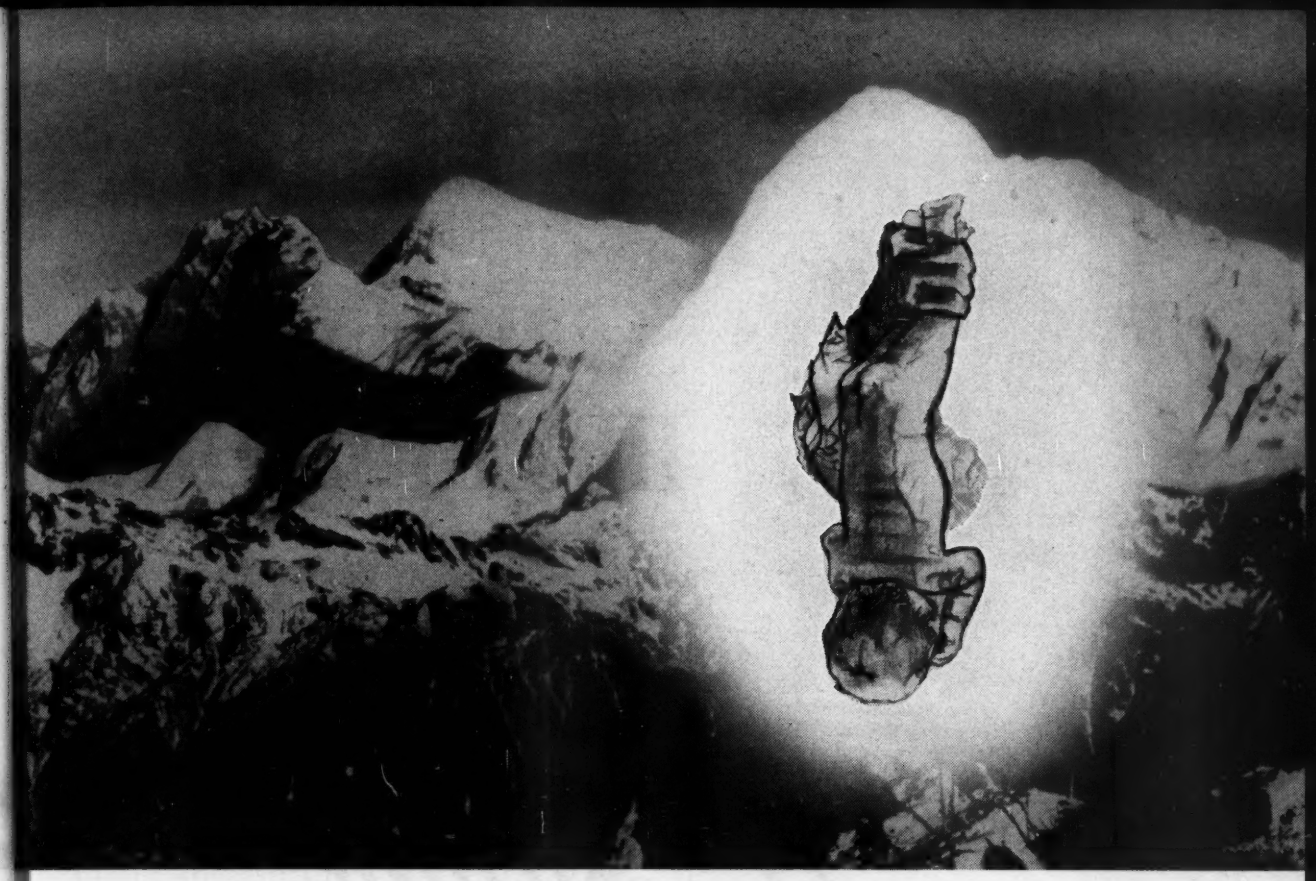

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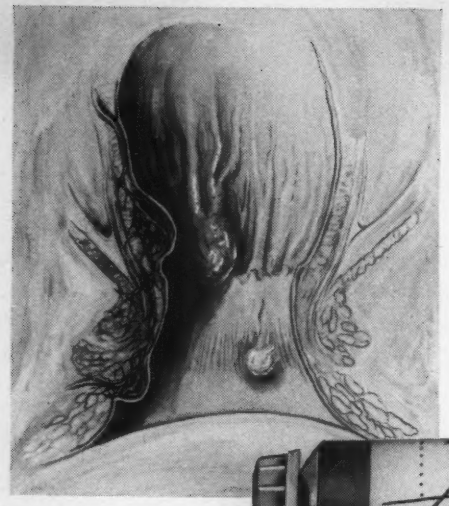

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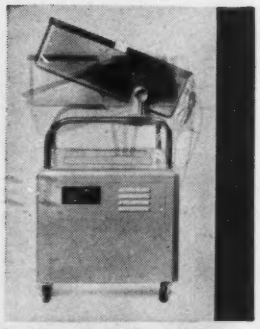

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(2) Karpovitch, P.: Adventures in Artificial Respiration, New York, Associated Press, 1953.
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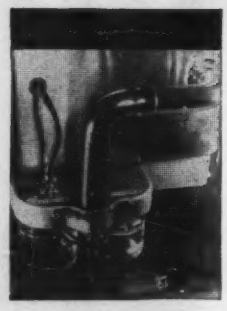

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To reduce the incidence of nausea and vomiting

The suggested dosage regimen consists in the administration of PHENERGAN Hydrochloride, 25 mg., orally the evening before surgery, followed by 1 to 2 cc. (25 to 50 mg.) of Injection PHENERGAN Hydrochloride on call to the operating room the day of surgery.

TABLETS INJECTION

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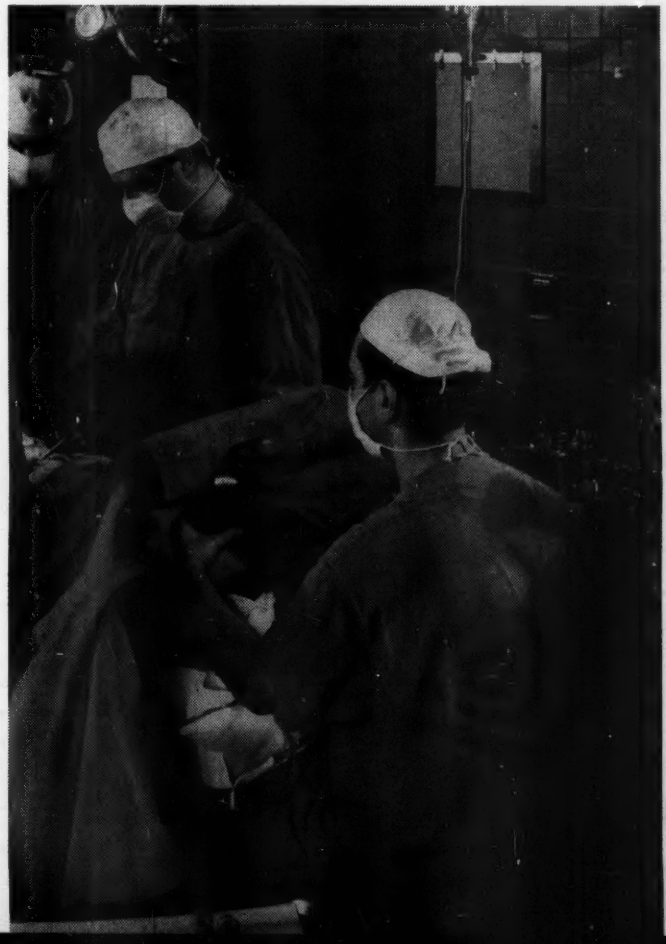
Promethazine Hydrochloride, Wyeth



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PROVIDES NEW RELIEF OF SURFACE PAIN AND ITCHING ON CONTACT WITHOUT TOUCHING AFFECTED AREAS

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pruritus vulvae
wounds
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FORMULA: benzocaine 4.7%; benzethonium chloride 0.1%; menthol 0.5%; dissolved in oils (Doho process)

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Contain calcium...
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She's pregnant, but she's active, travelling—on the go every day. That's why she needs a vitamin-mineral supplement generously formulated for the stress of pregnancy.

Natalins-PF are formulated for the busy, modern woman. The capsules are small, attractive, easy to swallow. Just one to three capsules daily, according to need, help supply the increased requirements for vitamins, iron and calcium in pregnancy.

For some patients, you may prefer to prescribe Natalins® which contain *both* calcium and phosphorus.

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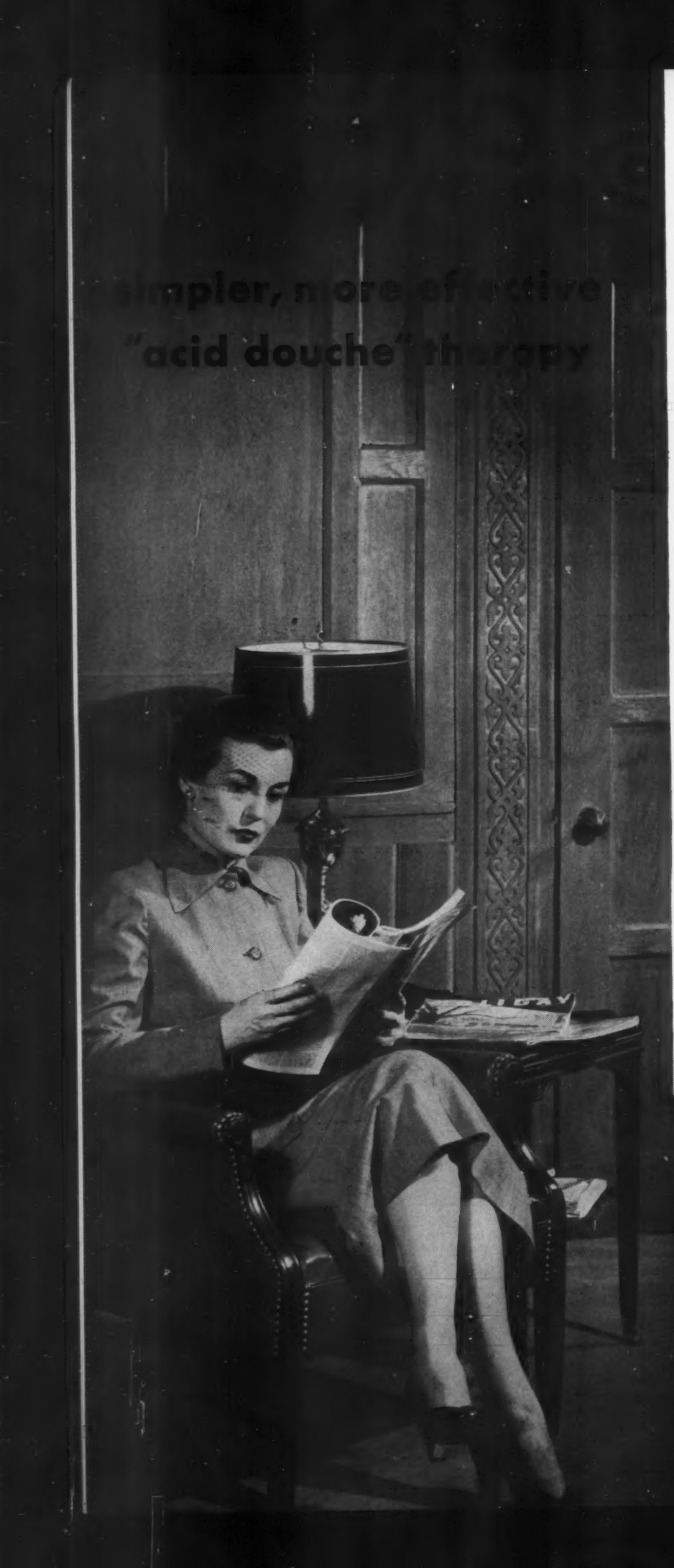

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to restore
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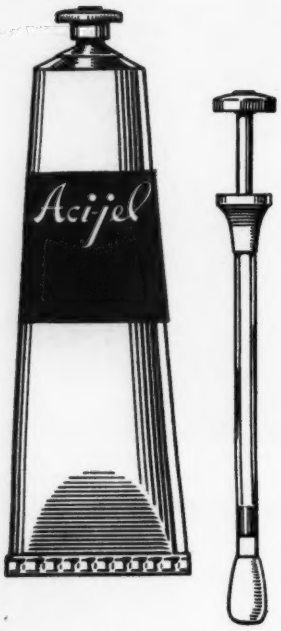

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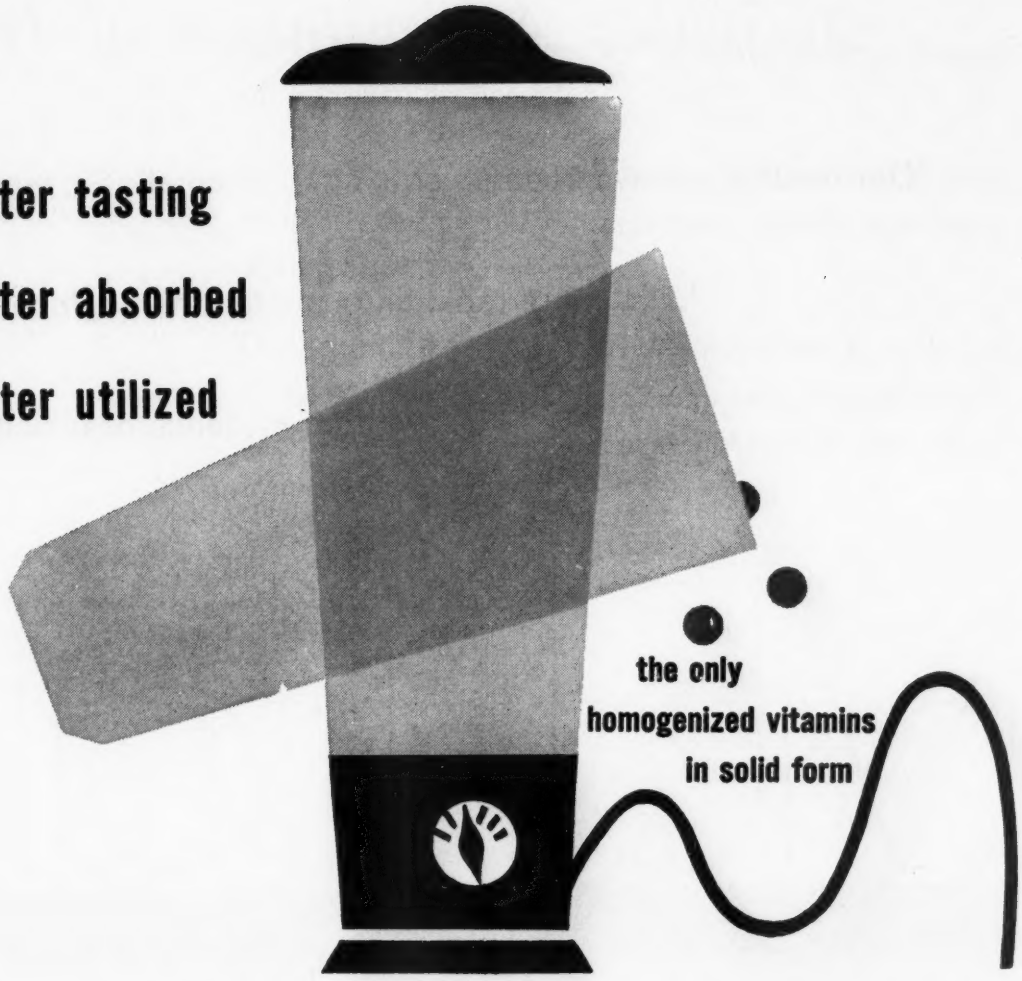

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". . . a more rapid and constant hemoglobin rise

. . . with no evidence of toxicity."[2]

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Now

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*Better tolerated Mol-Iron is now available with vitamin C (75 mg. per tablet), because ascorbic acid has been shown to promote increased absorption of orally administered iron.[15]

Dosage: Adults—2 tablets t.i.d. after meals.
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Supplied: Bottles of 100 only.

Well-tolerated—even by patients with a history of iron intolerance.[3, 4]

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Outstanding efficacy and tolerance is attested by more original investigations and clinical evaluations[1-14] than have been reported for any other iron preparation.

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REFERENCES:

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Dosage: Adults—2 tablets t.i.d. after meals.
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Supplied: Tablets in bottles of 100. Liquid in bottles of 12 fluid oz. Drops in bottles of 15 and 50 cc. with calibrated dropper.

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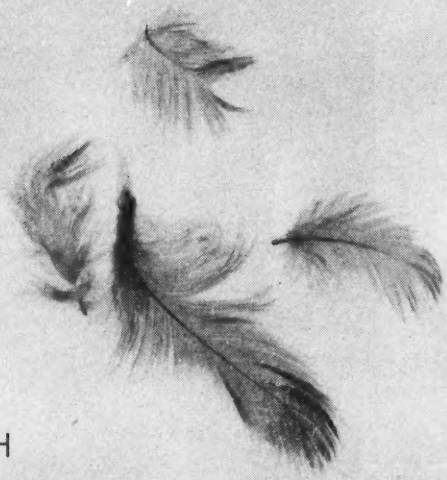

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"Gentleness in handling fragile tissues must be mastered, and the feather touch is essential."

Potts, W. J.: J. A. M. A. 157:627 (Feb. 19) 1955, p. 629.

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(VITAMIN K_1, MERCK)

"... vitamin K_1 is more effective than any other agent now available in combating drug-induced hypoprothrombinemia."[1] "Vitamin K_1 appears to be equally effective by the oral or intravenous route."[2] Beneficial effects are apparent in 6 to 10 hours following oral use.

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References: 1. Gamble, J.R., et al. Arch. Int. Med. 95:52, 1955. 2. Gamble, J.R., et al. J. Lab. & Clin. Med. 42:805, 1953.

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extra protection for every conception

Hesper-C Prenatal

with capillary-protective factors

a precaution in normal pregnancy *a necessity* in habitual abortion[1,2]

The problem of spontaneous abortion is not limited to habitual aborters. It is estimated that 10% to 20% of *all* pregnancies end in spontaneous abortion. Studies by Greenblatt,[1,3] Javert[4,5] and Dill[2] have revealed that integrity of the decidual vessels is a key to successful completion of pregnancy . . . and confirm that hesperidin complex and ascorbic acid, provided by Hesper-C Prenatal, restore and maintain capillary integrity.[6,7]

In several groups of habitual aborters, these researchers effected substantial fetal salvage—as high as 95% in one series[4]—when Hesper-C (hesperidin complex and ascorbic acid) was added to a regimen of prenatal supplementation and therapy.

Only Hesper-C Prenatal gives your patients the extra protection of hesperidin complex and ascorbic acid, plus the established prenatal vitamin-mineral supplementation, at a nominal increase in daily cost.

Hesper-C Prenatal is the only *complete* supplement for *all* your pregnant patients.

Each capsule contains:

Hesperidin Complex	100 mg.	Vitamin B_{12}	0.75 micrograms
Ascorbic Acid	100 mg.	Folic Acid	0.05 mg.
Vitamin A Acetate	1000 U.S.P. units	Pyridoxine Hydrochloride	1.67 mg.
Vitamin D_2	200 U.S.P. units	Calcium Pantothenate	1.0 mg.
Thiamine Mononitrate	1.25 mg.	Ferrous Gluconate (2.5 mg. iron)	21.6 mg.
Riboflavin	0.75 mg.	Calcium Carbonate (83.3 mg. calcium)	208.25 mg.
Nicotinamide	5.0 mg.	Copper Sulfate (0.5 mg. copper)	2.0 mg.
		Potassium Iodide (0.05 mg. iodine)	0.065 mg.

In bottles of 100 and 500 capsules.

Recommended daily dose: Two capsules t.i.d.
Providing the daily requirements or more of vitamins and iron during pregnancy as recommended by the National Research Council.

References: 1. Greenblatt, R. B.: Obst. & Gynec. *2*:530, 1953. 2. Dill, L. V.: M. Ann. District of Columbia *23*:667, 1954. 3. Greenblatt, R. B.: Ann. New York Acad. Sc. *61*:713, 1955. 4. Javert, C. T.: Obst. & Gynec. *3*:420, 1954. 5. Javert, C. T.: Ann. New York Acad. Sc. *61*:700, 1955. 6. Barishaw, S. B.: Exp. Med. & Surg. *7*:358, 1949. 7. Selsman, G. J. V., and Horoschak, S.: Am. J. Digest. Dis. *17*:92, 1950.

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Nipple fissures

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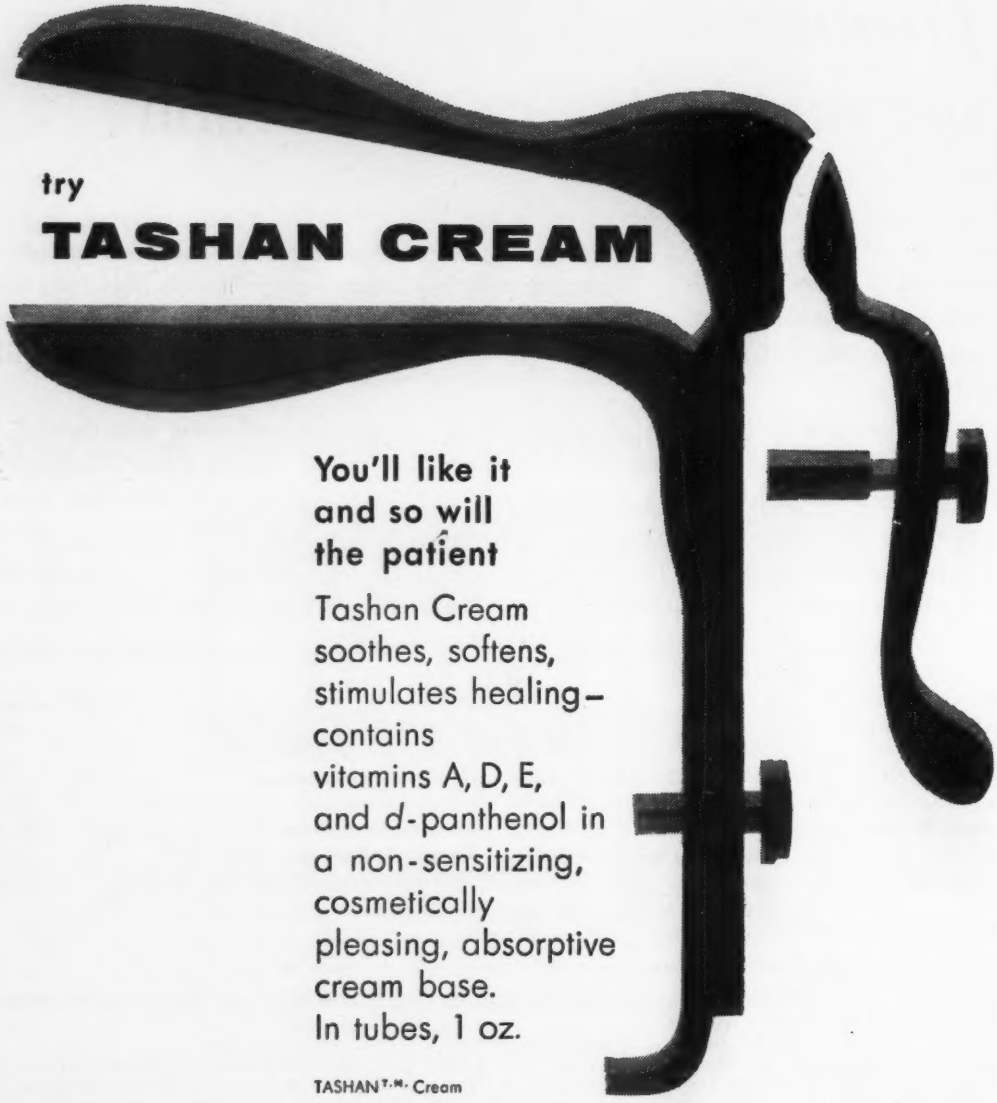

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In tubes, 1 oz.

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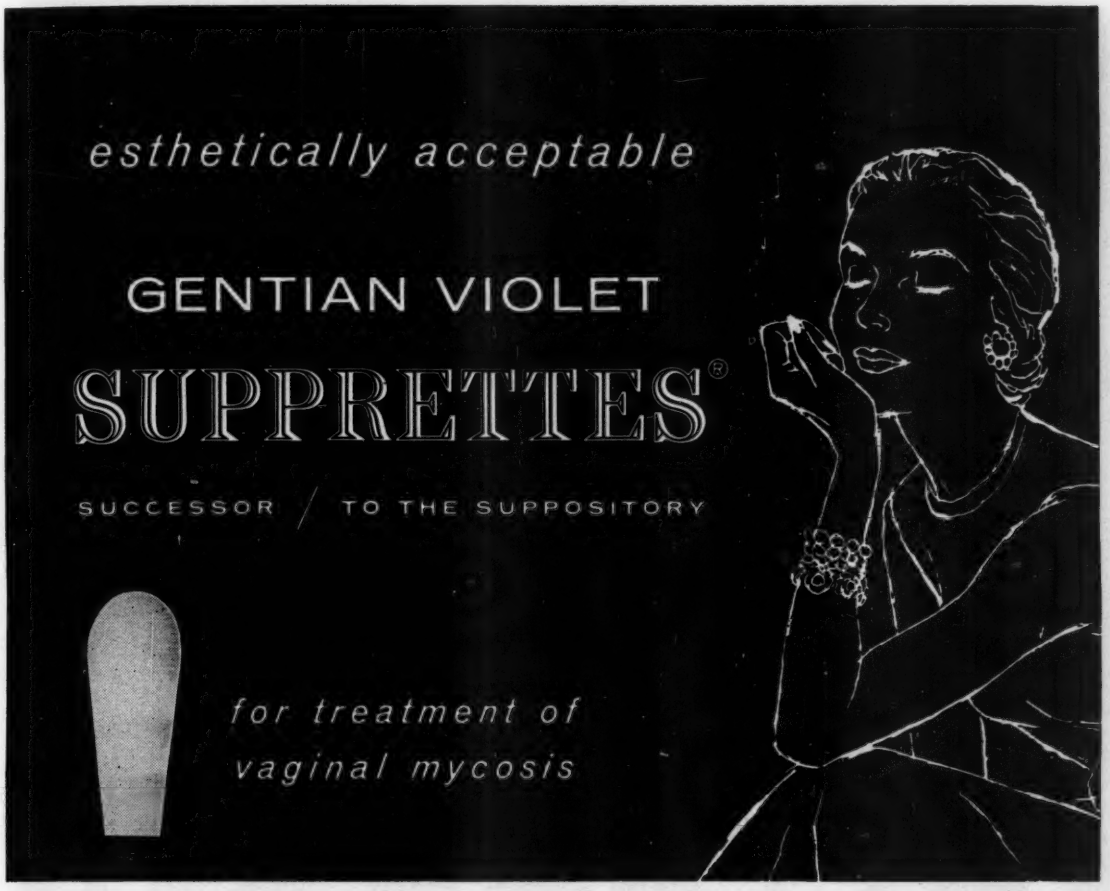

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Composition: Each Supprette contains gentian violet 0.2%, lactic acid 0.3%, and acetic acid 1.0%.
Supplied: In jars of 12.

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The "Neocera" Base Makes the Difference

Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent. Mixes completely with vaginal and cervical fluids to assure thorough penetration into folds of vaginal wall.

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Safety First in control of Nausea of Pregnancy

The first thought of every physician during the prenatal period is the safety of the patient.

The first choice of the physician for an agent to control nausea and vomiting will be EMETROL® when he considers the following advantages:

1. EMETROL does not contain barbiturates, bromides, antihistamine compounds, or any other drugs likely to induce untoward effects.
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SAFE

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(Phosphorated Carbohydrate Solution)

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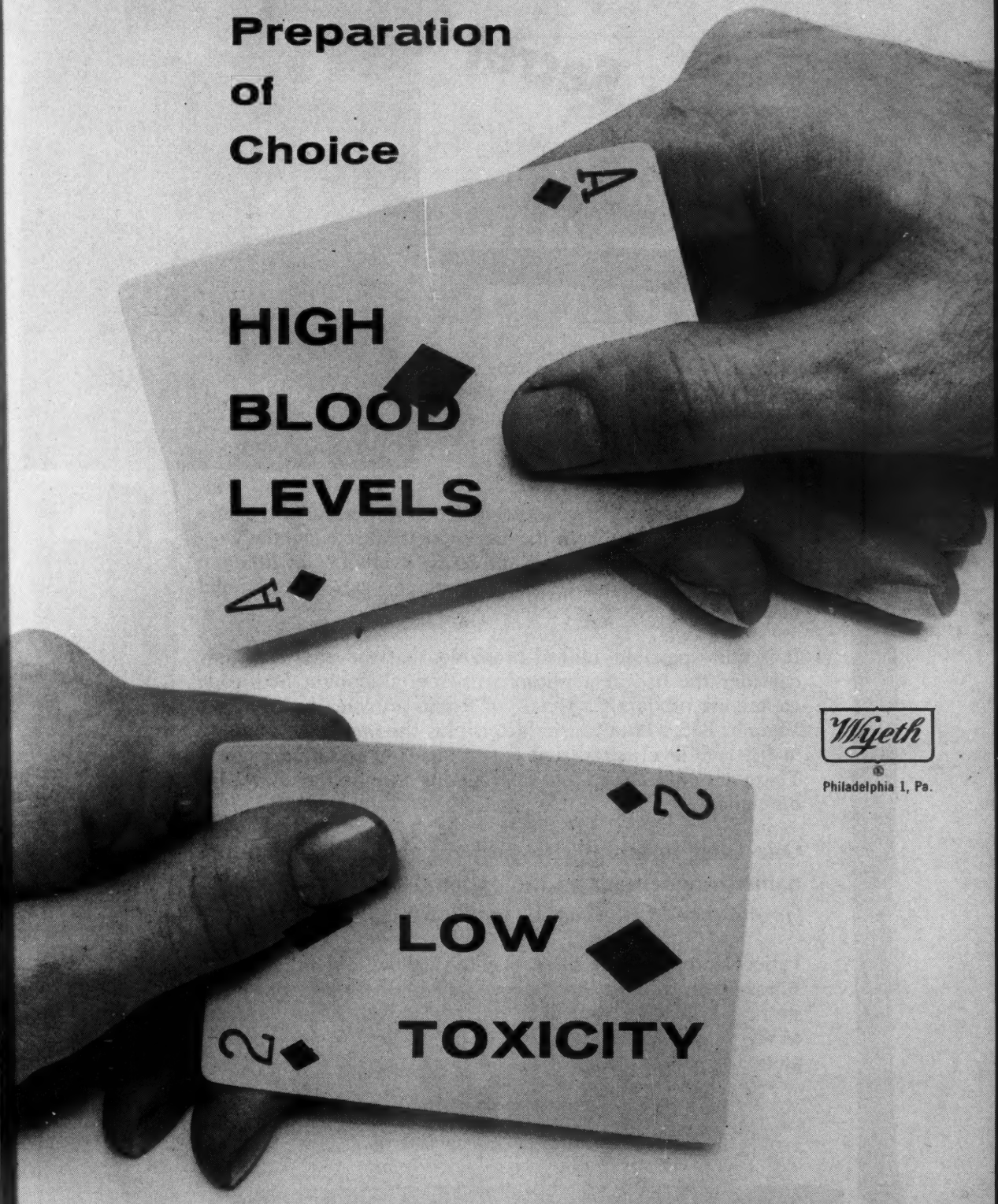

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SUSPENSION TABLETS

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Triple Sulfonamides
(Sulfadiazine, Sulfamerazine, Sulfamethazine)

I've Got a Secret

It's probably that he has a frog in his pocket... but his mother also has a secret... she's going to have a baby.

This intelligent modern mother has placed herself in the care of the physician in whom she has implicit faith. Now, the Doctor may, and probably does, prescribe a number of different prenatal supplements to his patients for various but valid reasons.

It is quite possible, indeed probable, that the physician may consider the use of a phosphorus-free, aluminum hydroxide containing product. Especially if it also provides organic iron, Vitamin B12 with intrinsic factor, plus the *important* vitamins in the *new* levels suggested for pregnant or lactating women. There are only a very *few* such quality formulas available for his choice.

One such formula with perhaps the easiest product name to remember on the national scene is Calcinatal® *(pronounced Calci' natal)* by Nion.

Patient acceptance of these easy-to-swallow tablets (not capsules) is quite understandable. Incidentally, one of your obstetrical problems, "control of Cramps" will be relegated to one of very minor incidence by use of the product. For more complete information, samples and brochure write to

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The satisfaction of knowing you have chosen the best is yours when you use B-P RIB-BACK blades.

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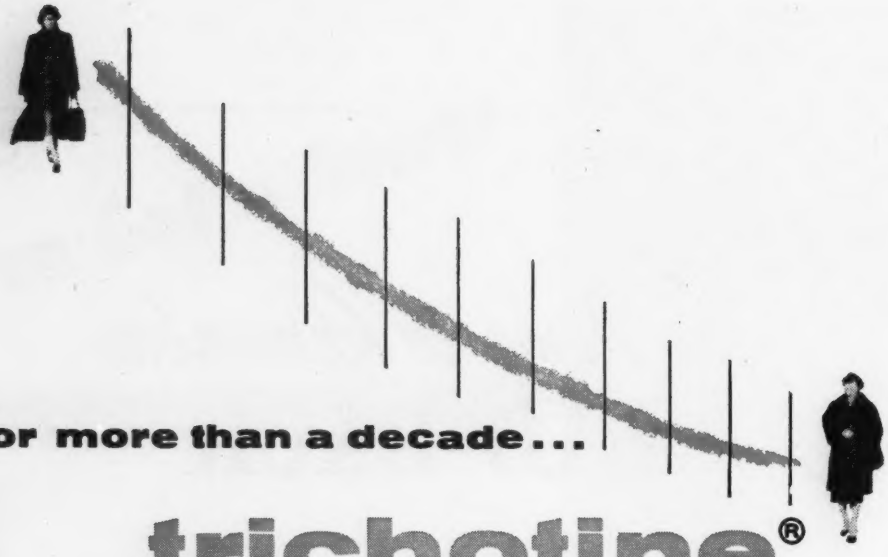
the 'only' RIB-BACK BLADE



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Trichotine douches may be prescribed as often as indicated—excellent also for postmenstrual or postcoital hygiene. Concentrated solutions are useful for clean-up or swab treatments in office. Hot packs are often quickly effective in pruritus vulvae.

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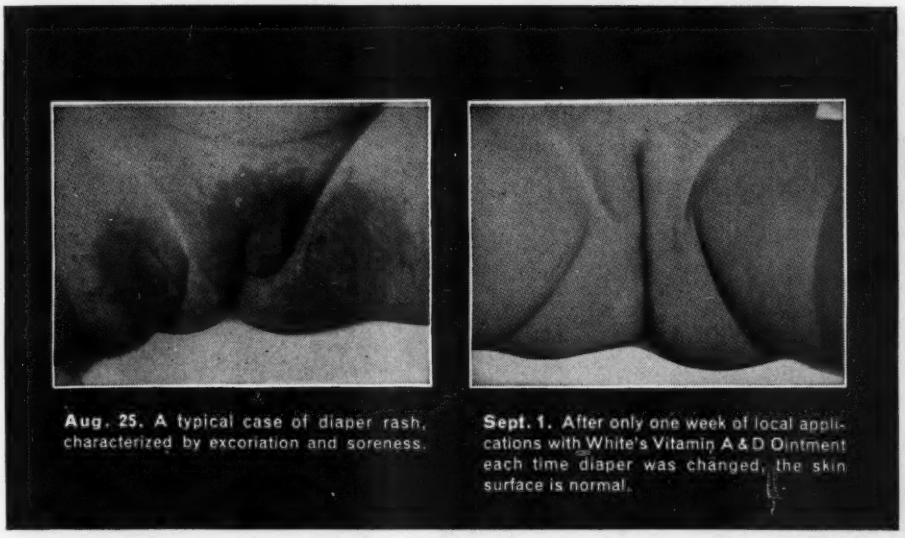

Aug. 25. A typical case of diaper rash, characterized by excoriation and soreness.

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White's Vitamin A & D Ointment

it's healing...soothing...protective.

Provides A & D vitamins in the same ratio as found in cod liver oil.

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- Massengill Powder solutions are easy to prepare. They are nonstaining, mildly astringent.

massengill powder®

when recommending a vaginal douche

indications:

Massengill Powder solutions are a valuable adjunct in the management of monilia, trichomonas, staphylococcus, and streptococcus infections of the vaginal tract. Routine douching with Massengill Powder solution minimizes subjective discomfort and maintains a state of cleanliness and normal acidity without interfering with specific treatment.

*In a recent clinical report, ambulatory patients —with an alkaline vaginal mucosa resulting from pathogens—maintained an acid vaginal mucosa of pH 3.5 for 4 to 6 hours after douching with Massengill Powder; recumbent patients maintained a satisfactory acid condition up to 24 hours.

*Arnot, P.H.: West. J. Surg., Obs., and Gyn. 62:85

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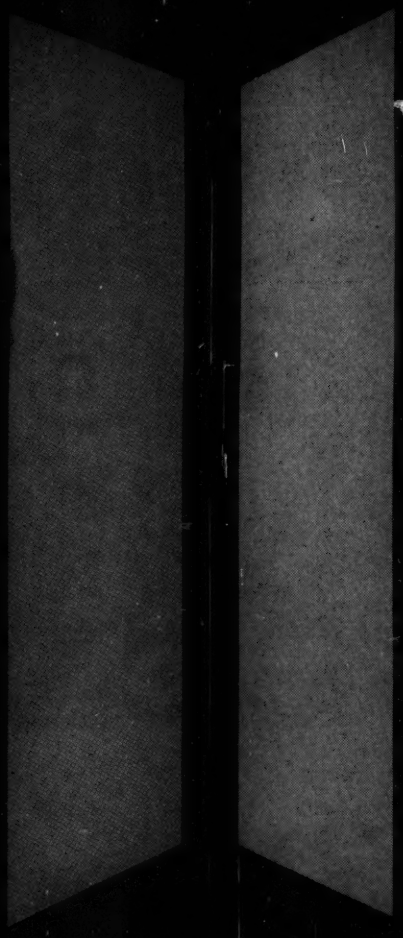

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1. Woodbridge, P.D.: J.A.M.A. *161*:644 (June 16) 1956.

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a unique <u>new</u> compound, ferrous calcium citrate, with tricalcium citrate

- iron and calcium in one molecule
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TABLETS

• a complete phosphorus-free prenatal supplement

Ortho

3 tablets daily provide:

Ferrous calcium citrate with tricalcium citrate	1500 mg.	Riboflavin (B_2)	3 mg.
Calcium	255 mg.	Niacinamide	30 mg.
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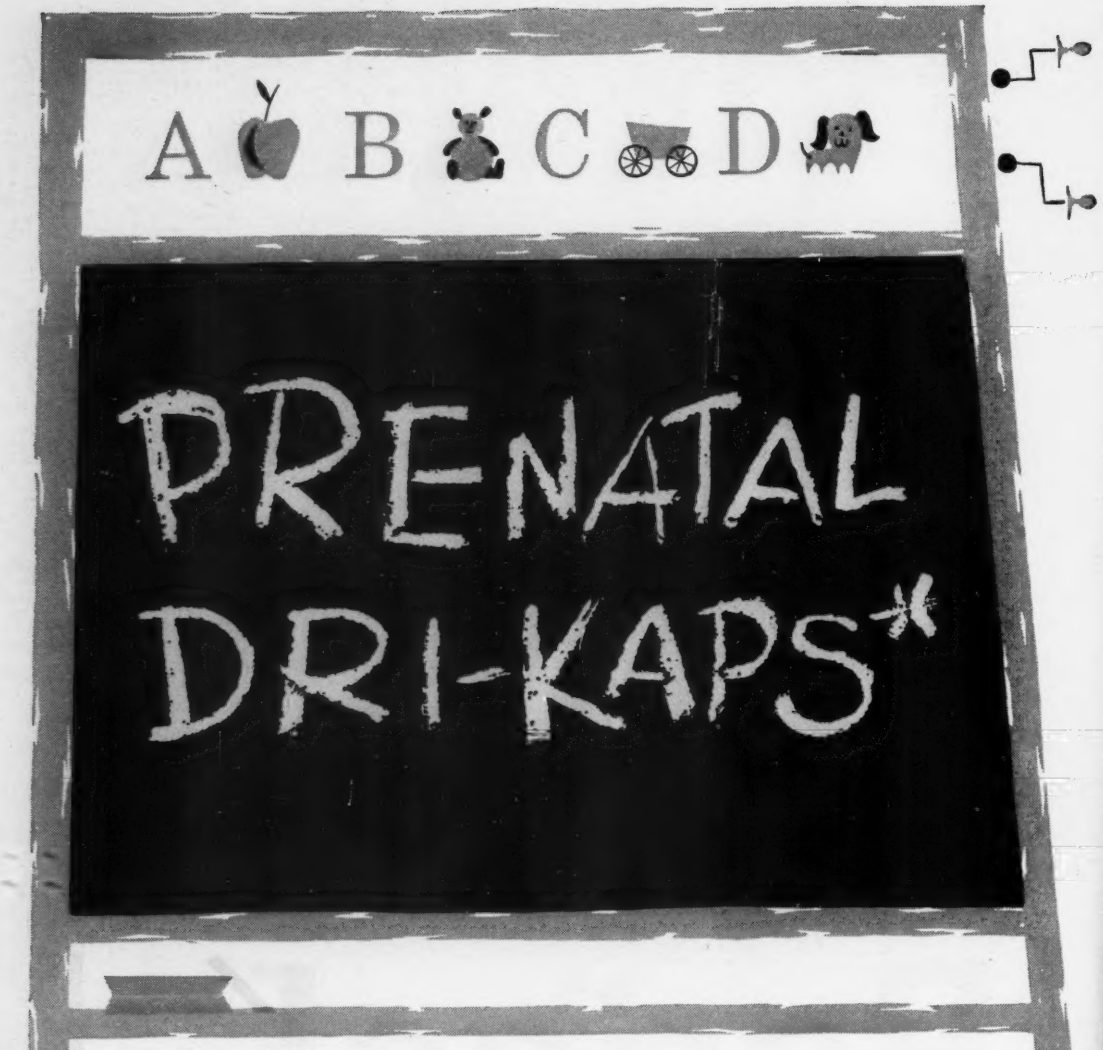
Vitamin A	6000 U.S.P. units	Pyridoxine hydrochloride (B_6)	3 mg.
Vitamin D	1200 U.S.P. units	Calcium pantothenate	6 mg.
Thiamine hydrochloride (B_1)	3 mg.	Vitamin B_{12}	3 mcg.
		Folic acid	1 mg.



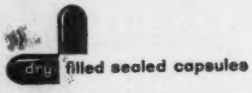
When you specify PRENATAL DRI-KAPS throughout pregnancy and lactation, your patients benefit by these Lederle features:

- comprehensive, balanced multivitamin-multimineral prenatal supplement (including three antianemia factors)
- exclusive DRI-KAP formulation—dry-filled sealed capsules assuring no oily repeat, no aftertaste (a Lederle exclusive)
- easy-to-swallow, convenient dosage
- made in Lederle's *own* laboratories under exacting quality control, your assurance of complete dependability

Each capsule contains:

Vitamin A	2000 U.S.P. Units
Vitamin D	400 U.S.P. Units
Thiamine Mononitrate (B_1)	2 mg.
Riboflavin (B_2)	2 mg.
Niacinamide	7 mg.
Vitamin B_{12}	1 mcgm.
Vitamin K (Menadione)	0.5 mg.
Ascorbic Acid (C)	35 mg.
Folic Acid	1 mg.
Calcium (in $CaHPO_4$)	250 mg.
Dicalcium Phosphate Anhydrous ($CaHPO_4$)	869 mg.
Iron (in $FeSO_4$)	6 mg.
Ferrous Sulfate Exsiccated	20 mg.
Manganese (in $MnSO_4$)	0.12 mg.
Phosphorus (in $CaHPO_4$)	190 mg.

Dosage: 1 to 3 capsules, throughout pregnancy and lactation.



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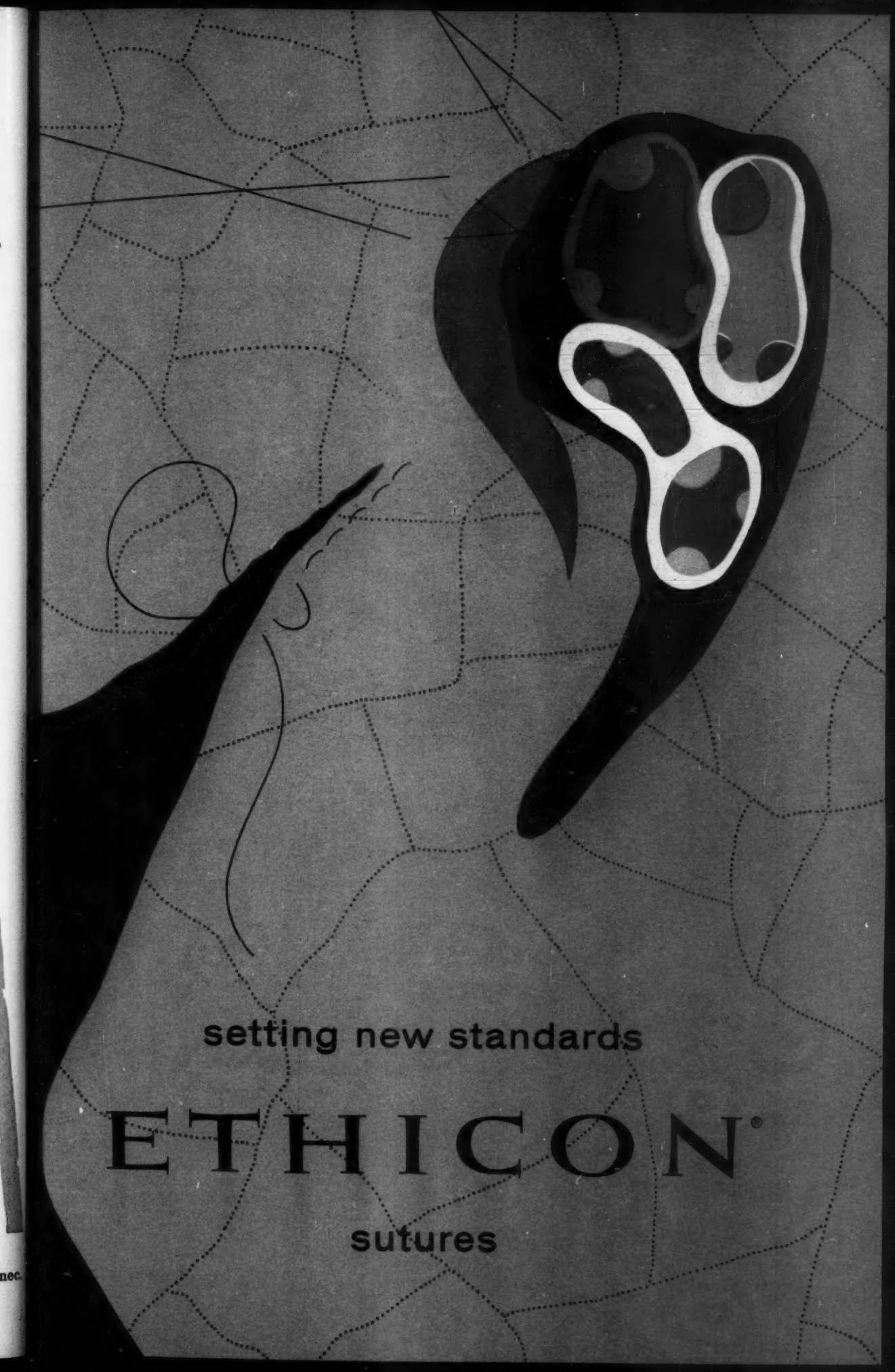
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Distinctive in its Chemistry: PRELUDIN is a totally new compound of the oxazine series.

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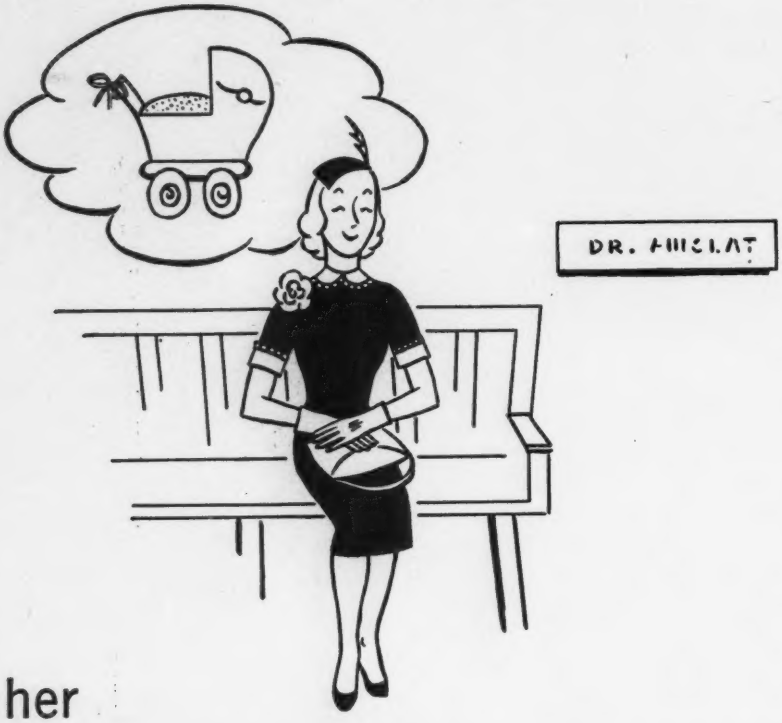

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. . . without nausea

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relieves nausea and vomiting and ***counteracts pyridoxine deficiency*** — ***in pregnancy***

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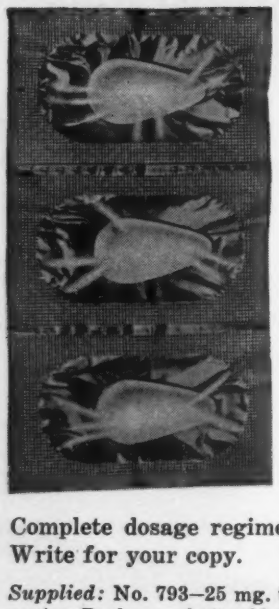

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because TACE (Chlorotrianisene)

is stored in "body banks"... the menopause is smoother

A

Section of rat omental fat containing TACE tagged with I^{131} (A) leaves radioautograph evidence (B) of TACE storage in body fat.

In a control study, I^{131} was administered *without* TACE. There was no evidence of the iodine in any of the body fat depots.

Radioautographs* prove unique TACE fat storage supporting fat bioassay findings of Greenblatt[1] and Thompson.[2]

*Tests performed for The Wm. S. Merrell Company by an independent radiological laboratory. Radioactive iodine supplied by the U. S. Atomic Energy Commission, Oak Ridge National Laboratory.

B

Prolonged relief for months after cessation of therapy.

An average duration of relief from menopausal symptoms of 2.95 months after discontinuance of TACE therapy has been reported.[3] The fat storage property of TACE is unique, and produces a clinical response free from the gross variations in estrogen stimulation common with other estrogens.[3]

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1. Long-acting — TACE is the only long-acting orally administered estrogen. **2.** Orally administered — TACE is administered only by mouth and is stored in body fat.[1] **3.** Inhibits pituitary activity — in experimental animals TACE has less tendency to produce pituitary hyperplasia than other estrogens.[5]

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In four series,[3,5-7] totaling 257 patients, 250 TACE-treated cases experienced no withdrawal bleeding... other side effects were minimal and TACE was well tolerated.

Average TACE Dosage: 2 capsules daily for thirty days. Severe cases may require additional short courses.

1. Greenblatt, R. B., and Brown, N. H.: Am. J. Obst. & Gynec. 63:1361, 1952. 2. Thompson, C. R., and Werner, H. W.: Proc. Soc. Exper. Biol. & Med. 77:494, 1951. 3. Woodhull, R. B.: Obst. & Gynec. Surv. 3:201, 1953. 4. Editorial: Management of the Menopause, J.A.M.A. 158:566, 1955. 5. Edwards, B. E.: J. Indiana M. A. 47:869, 1954. 6. Gillam, J. S.; Hunter, G. W., and Darne, C. B.: J. Clin. Endocrinol. 14:272, 1954. 7. Nulsen, R. O.; Carmon, W. B., and Hendricks, H. O.: Am. J. Obst. & Gynec. 65:1048, 1953.

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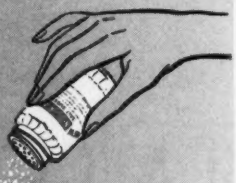

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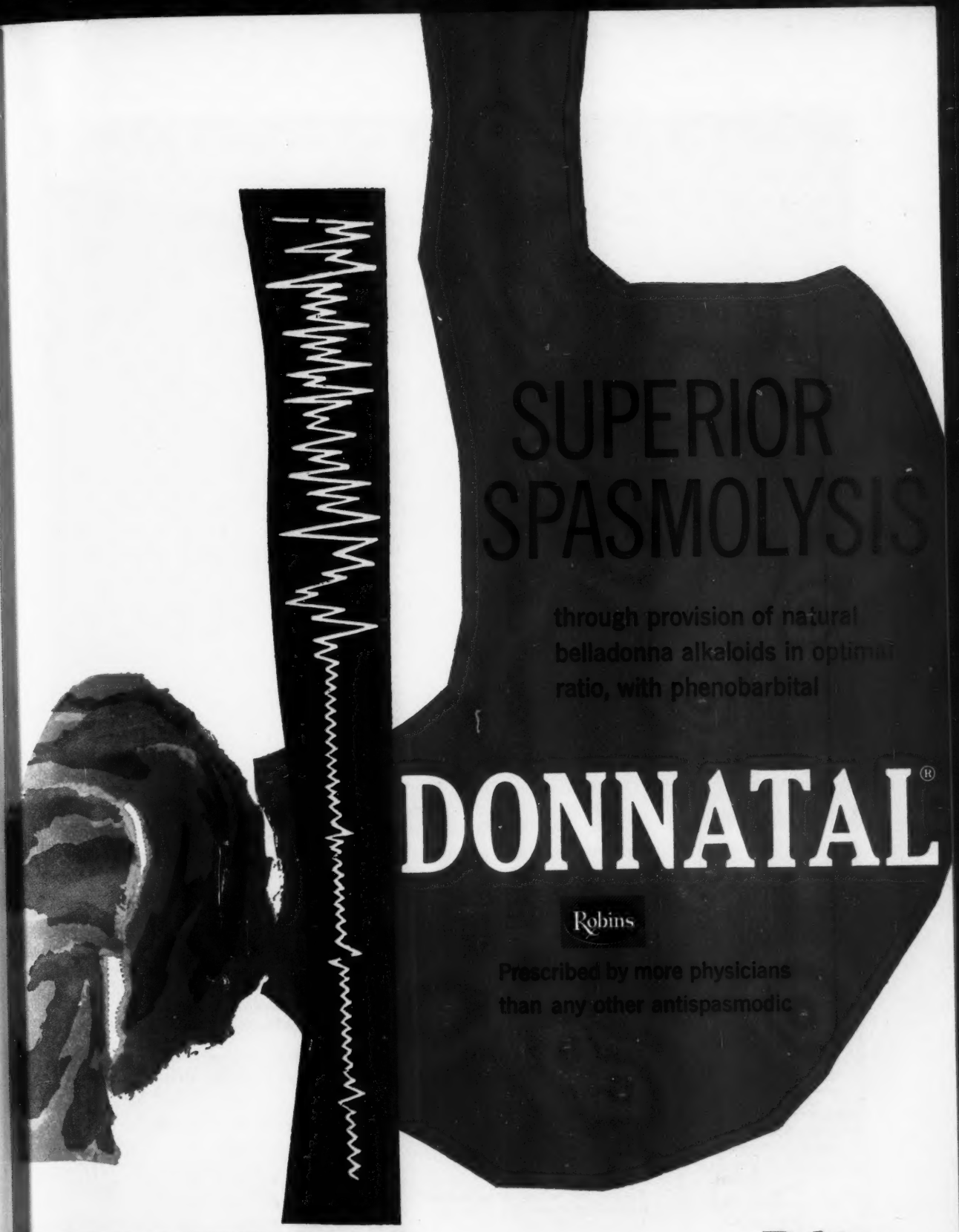

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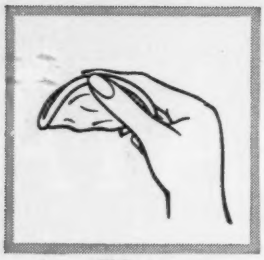

FIG. 1

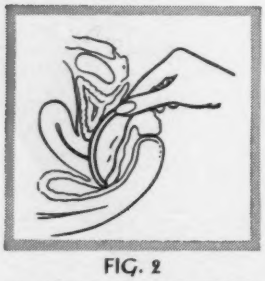

FIG. 2

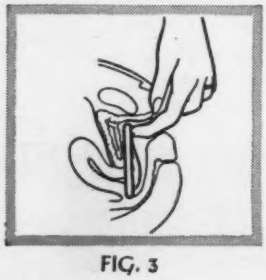

FIG. 3

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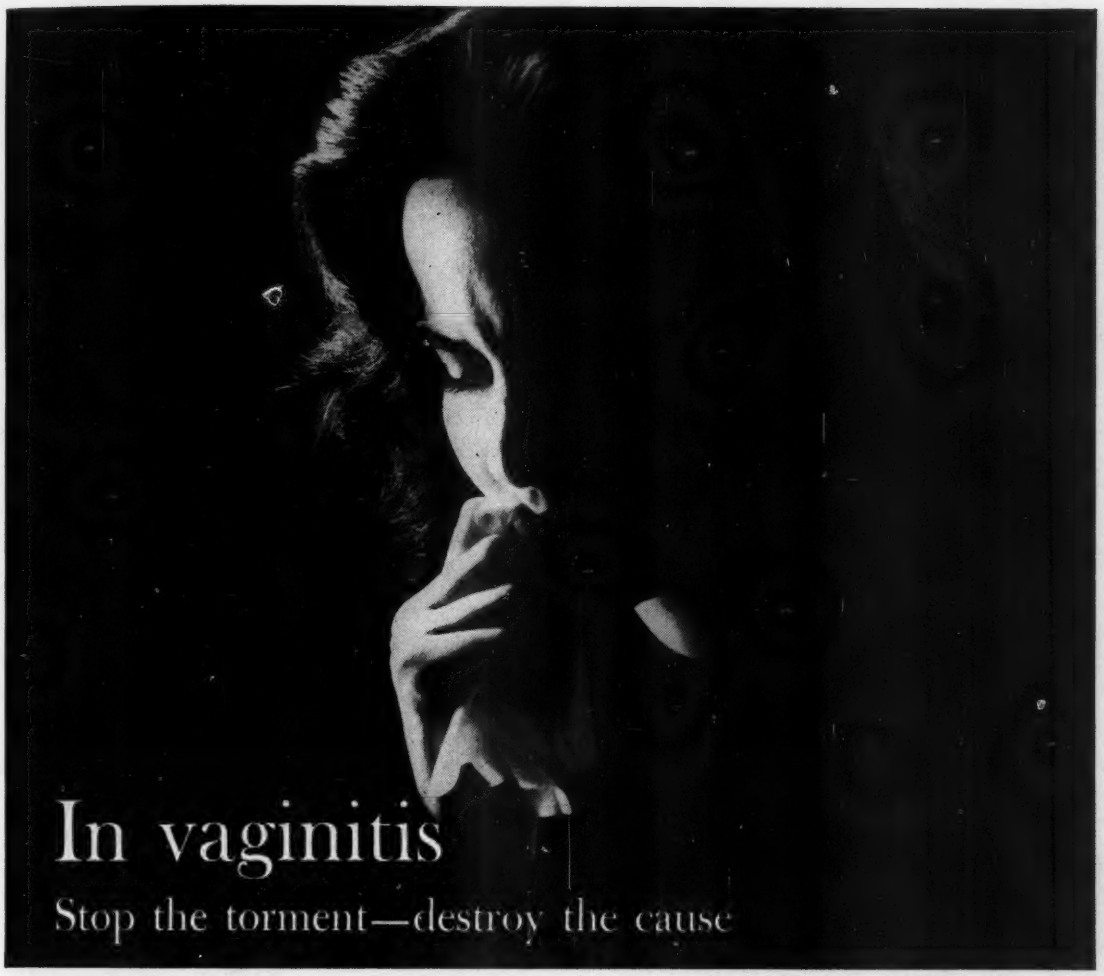

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Administration: An applicatorful twice daily—on arising and at bedtime.

Supplied: 4 oz. tubes with or without applicator.

(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Hensel, H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1946.

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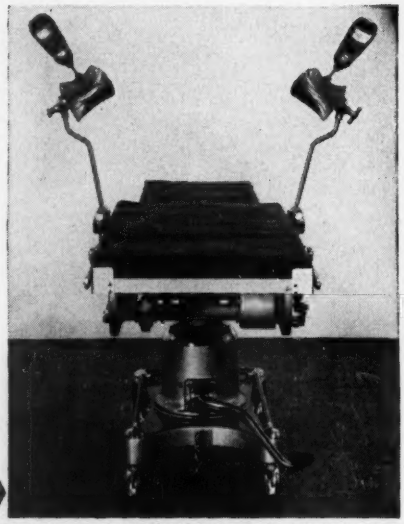

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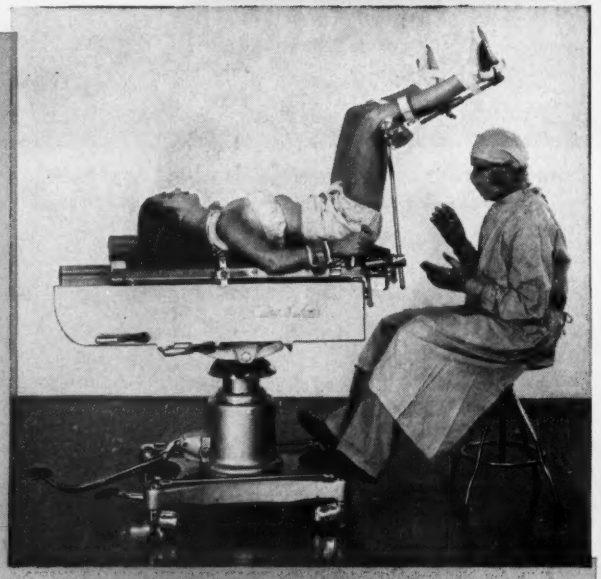

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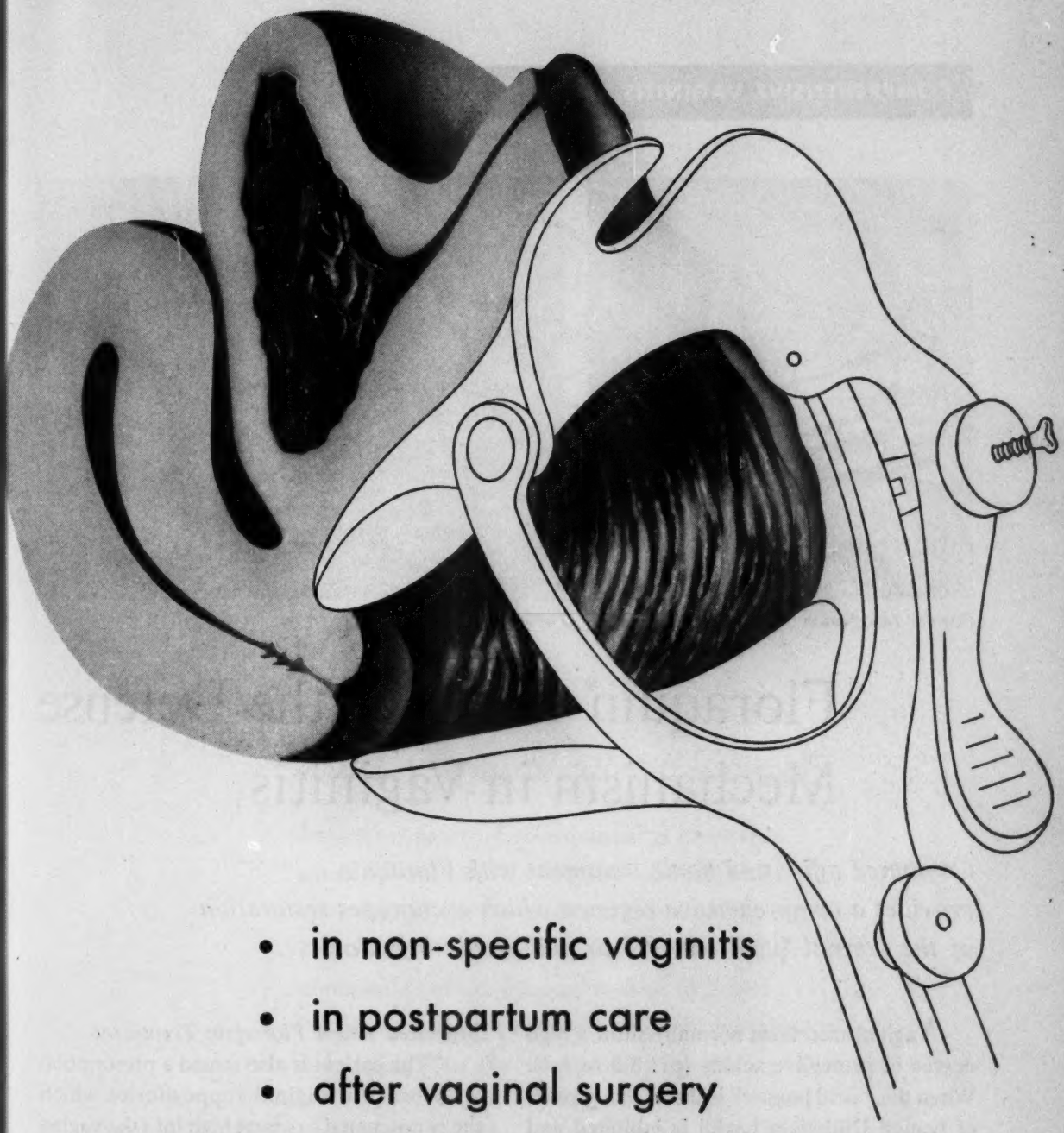

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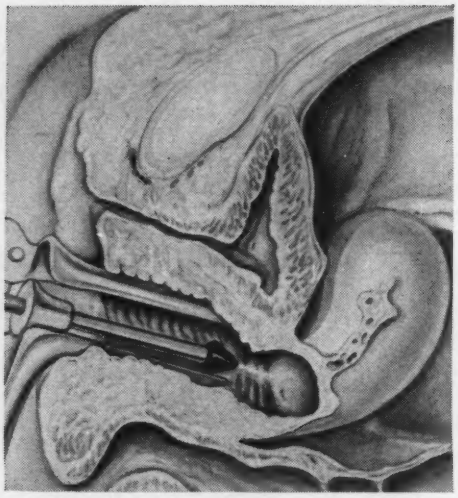

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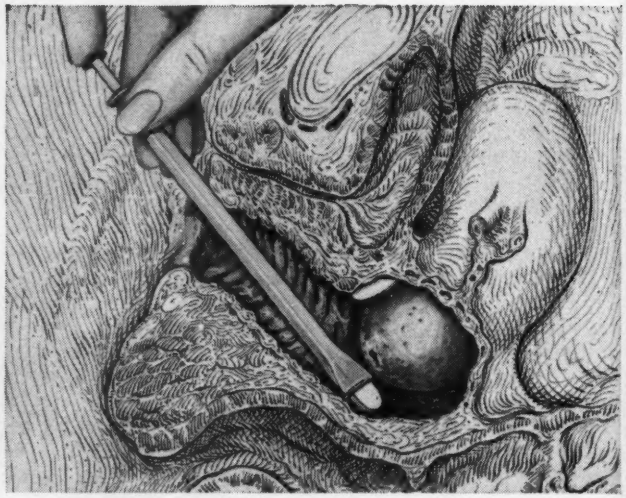

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*Williamson, P.: Trichomonad Infestation, M. Times *84*:929 (Sept.) 1956.

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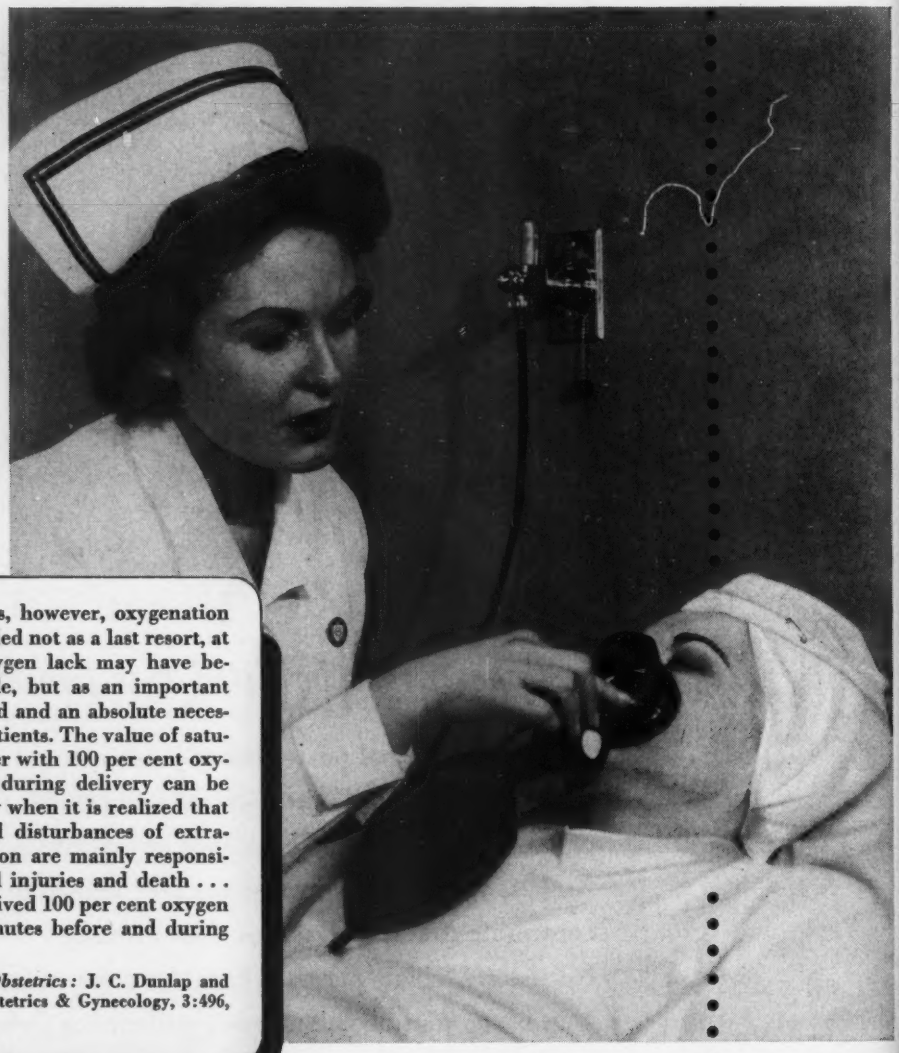

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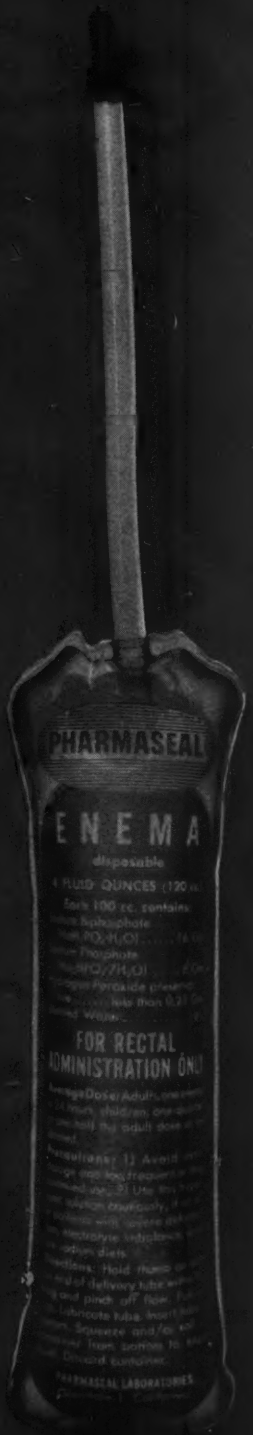

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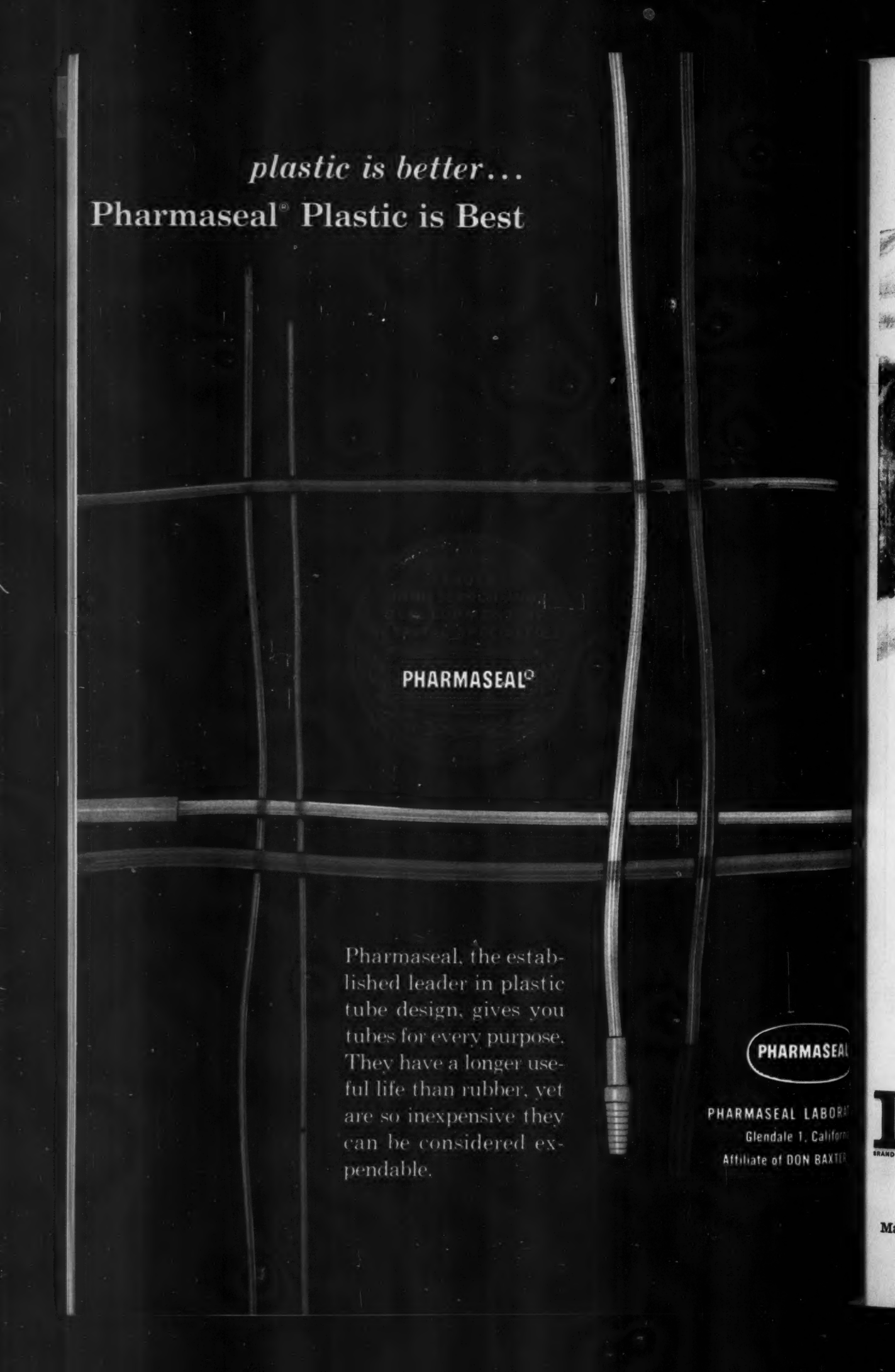
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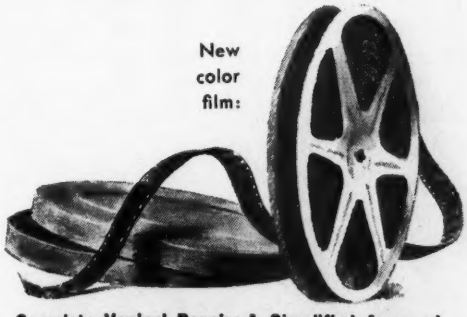

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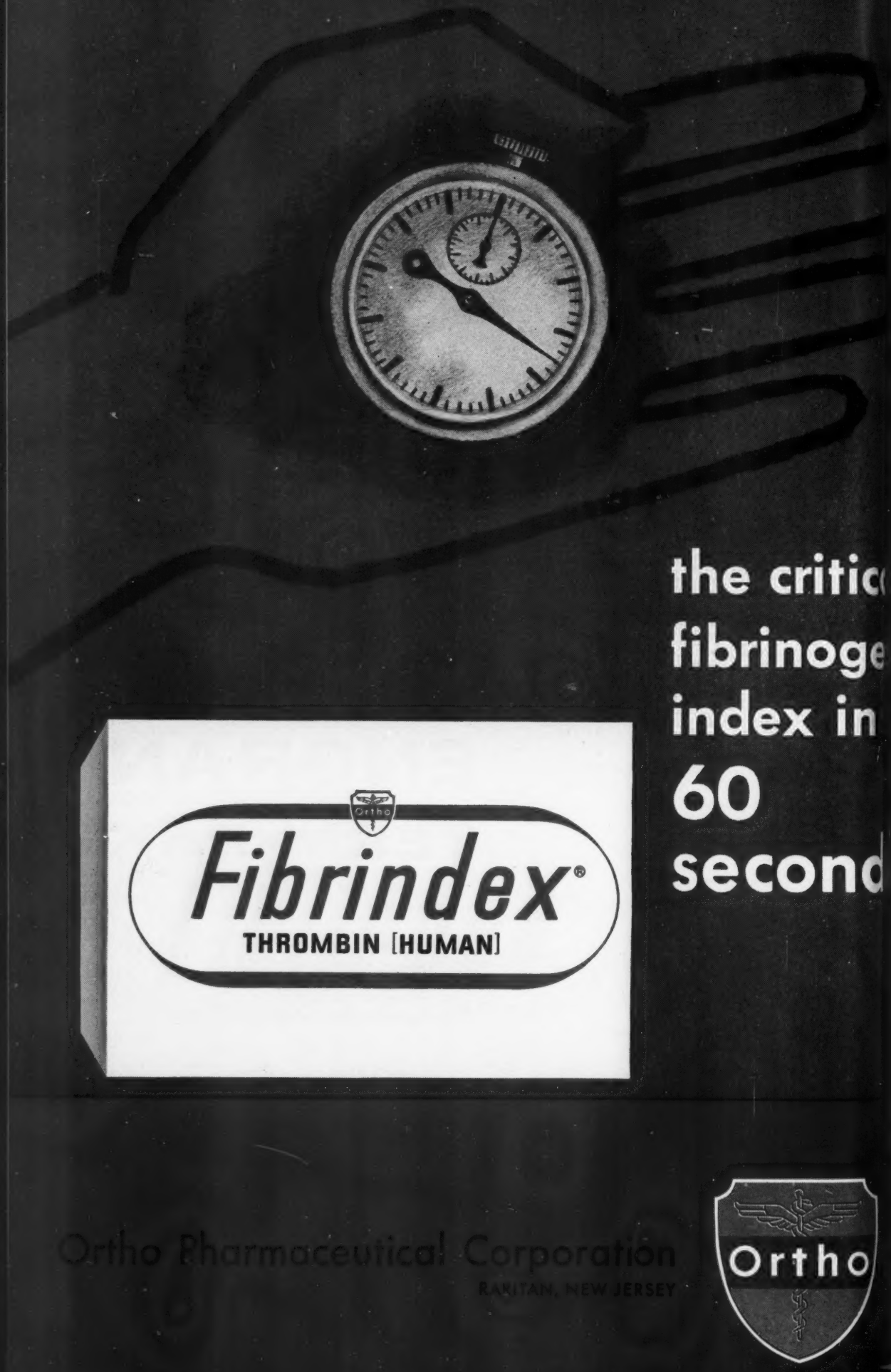
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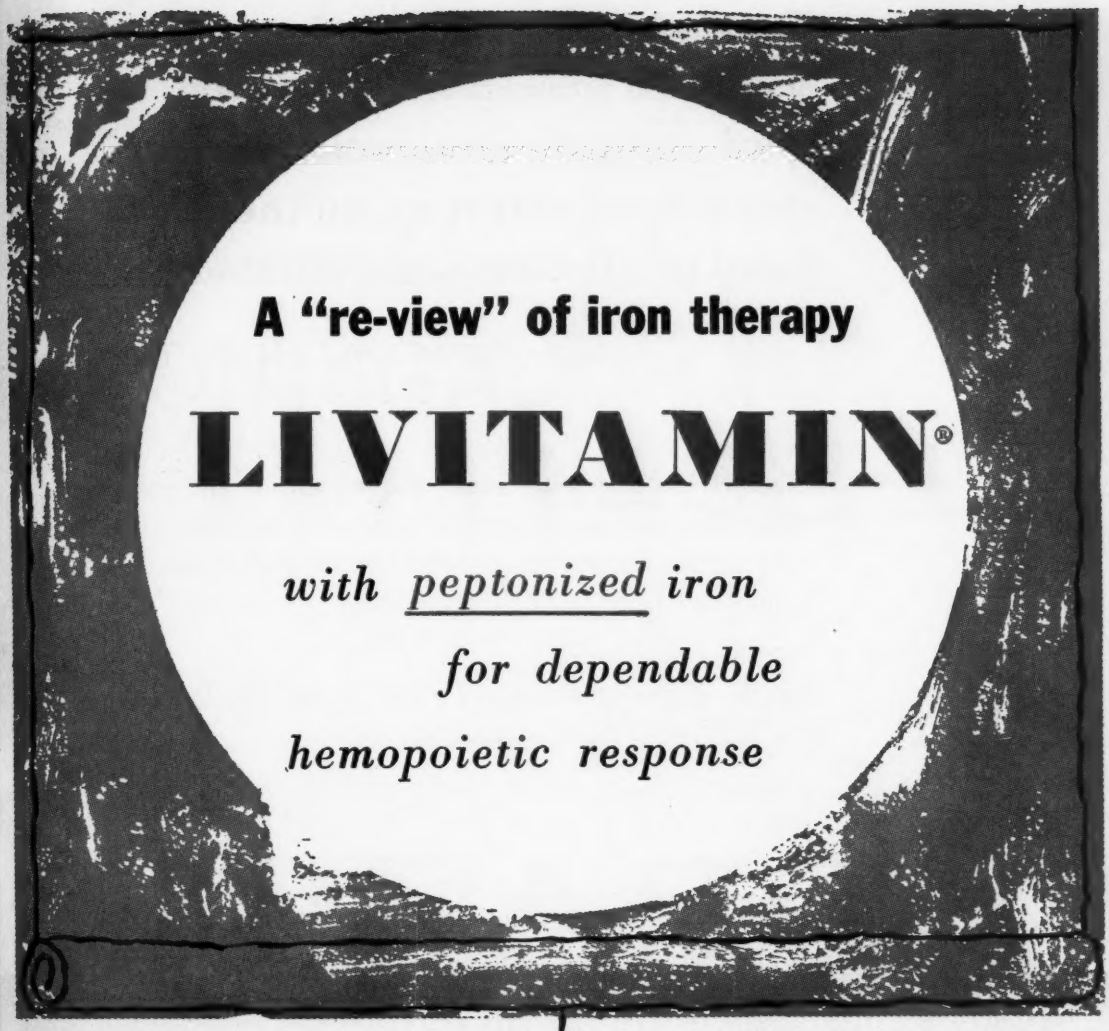

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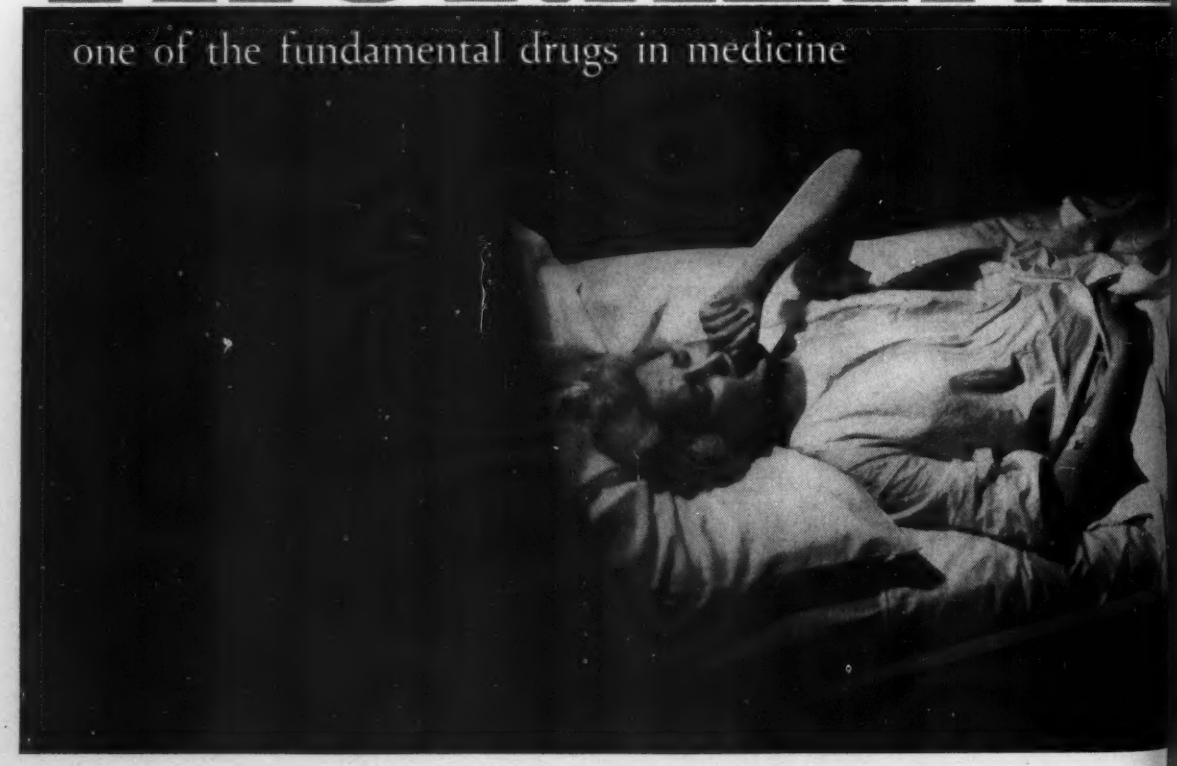

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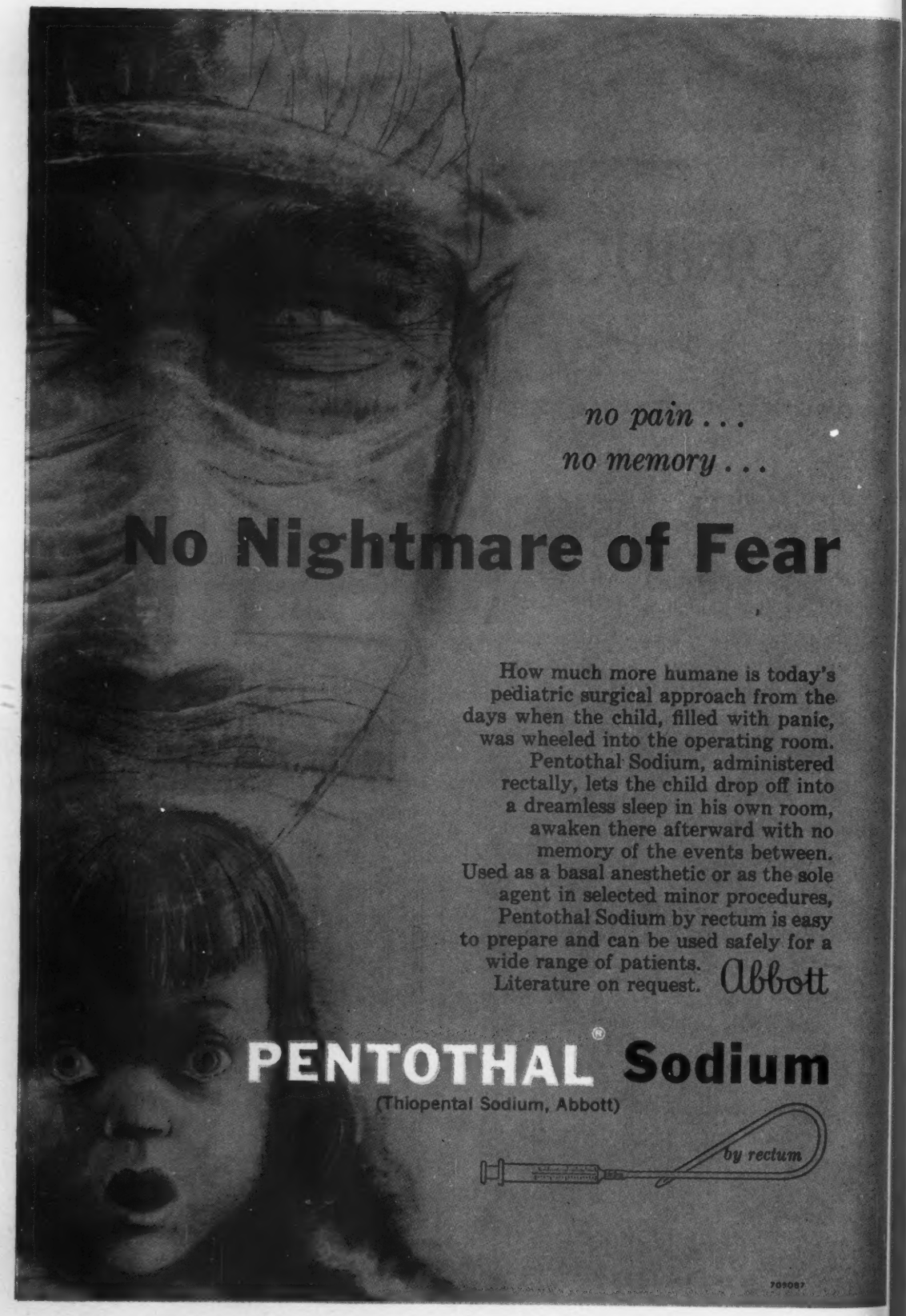
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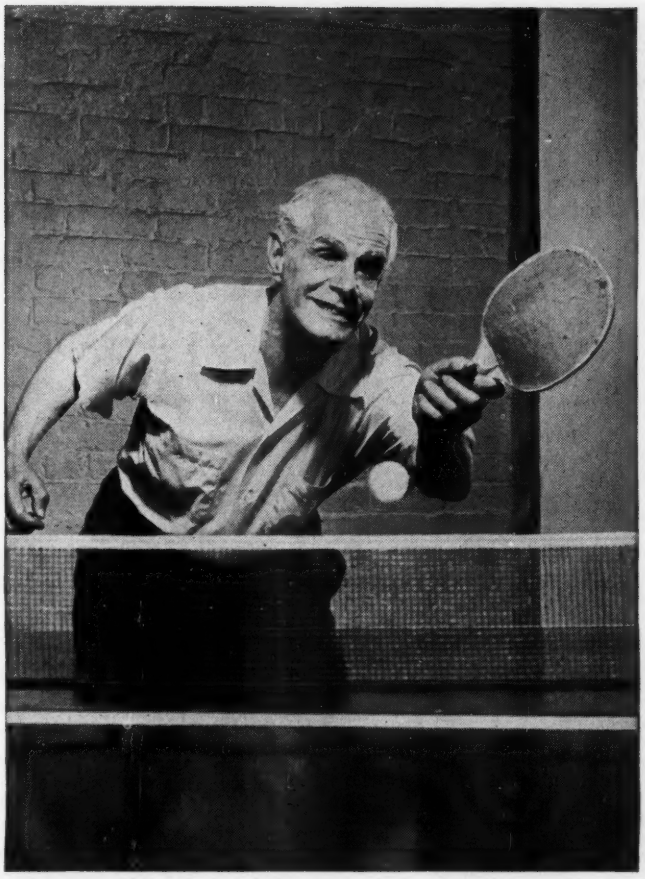

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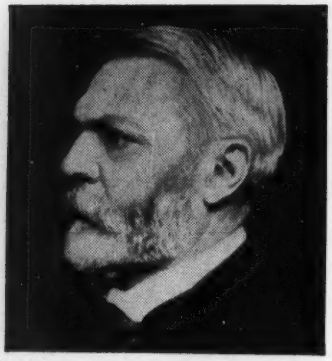

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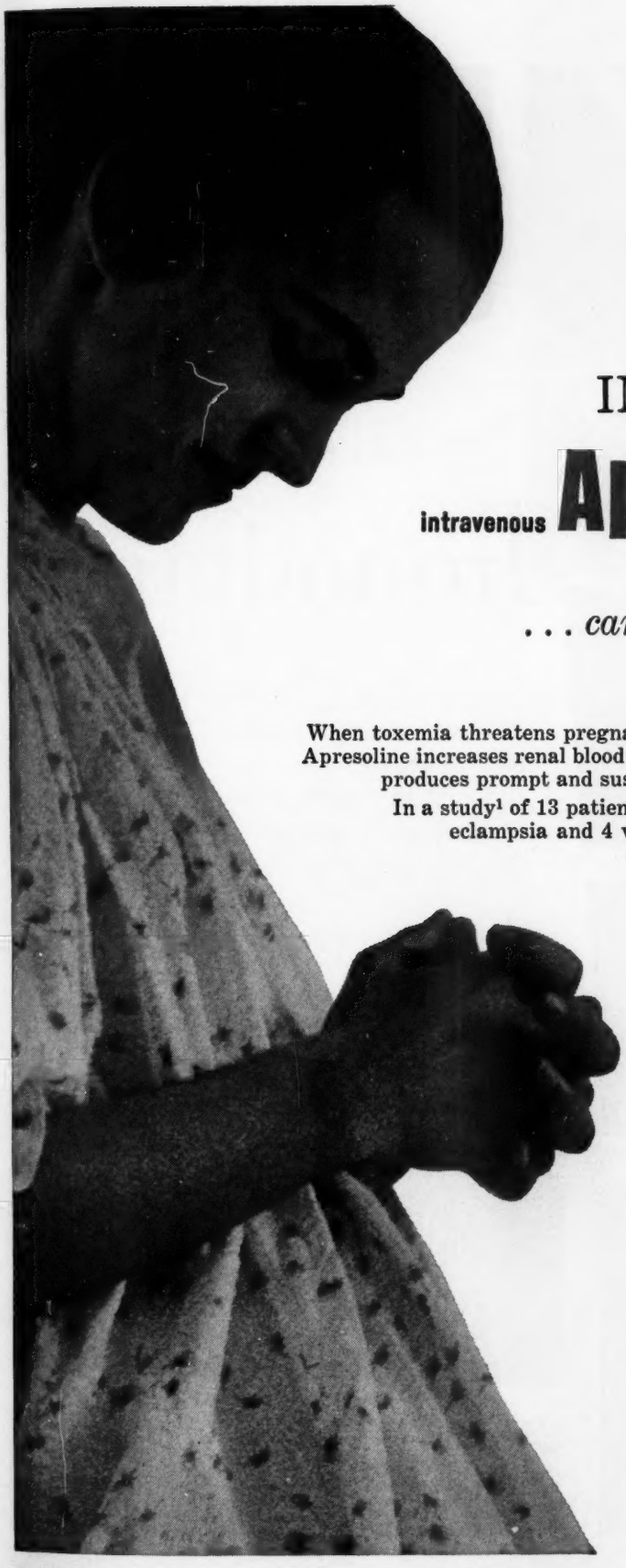

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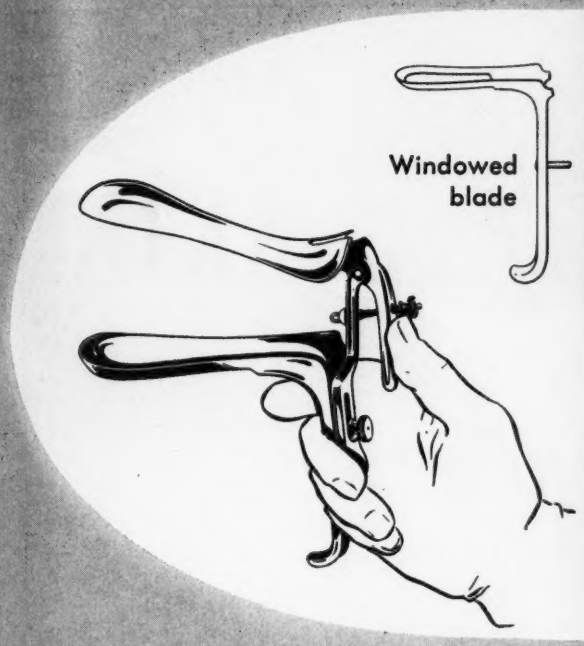

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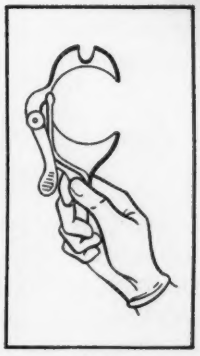

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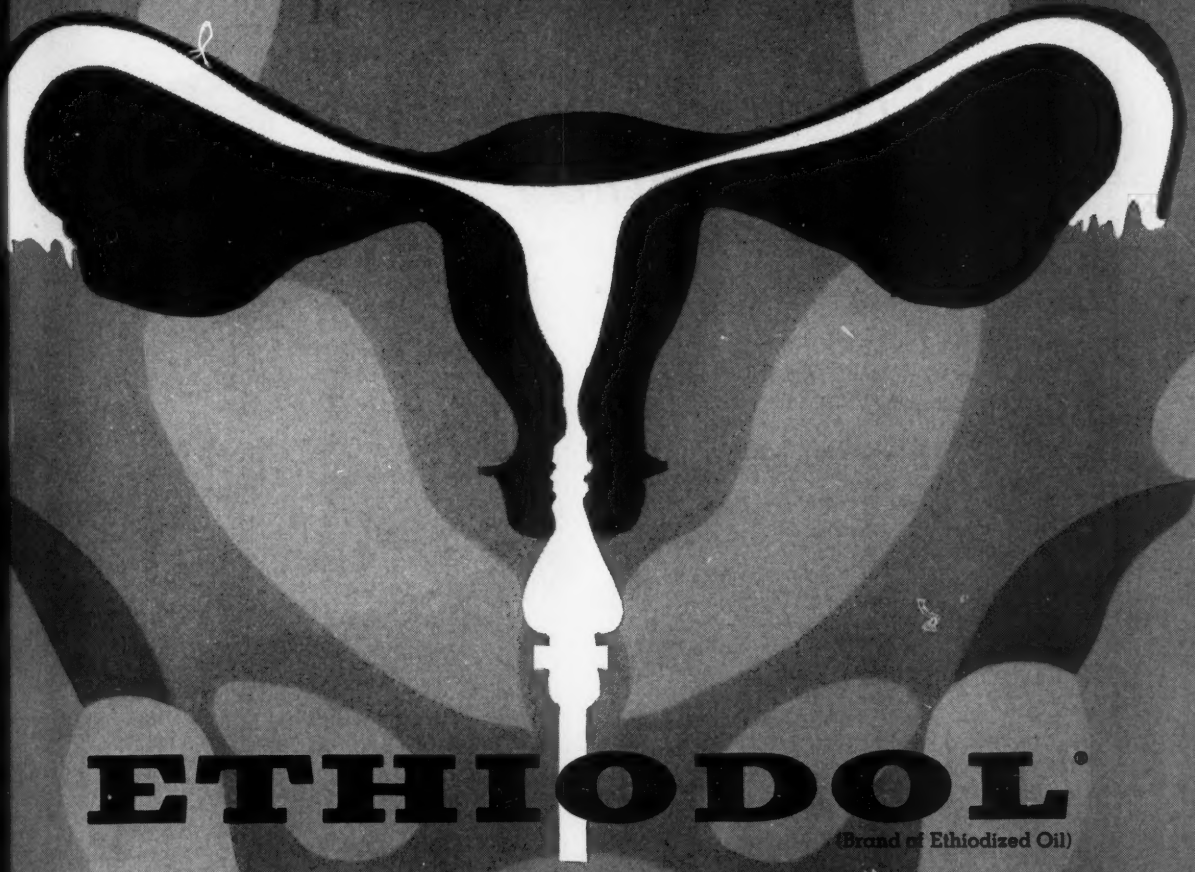

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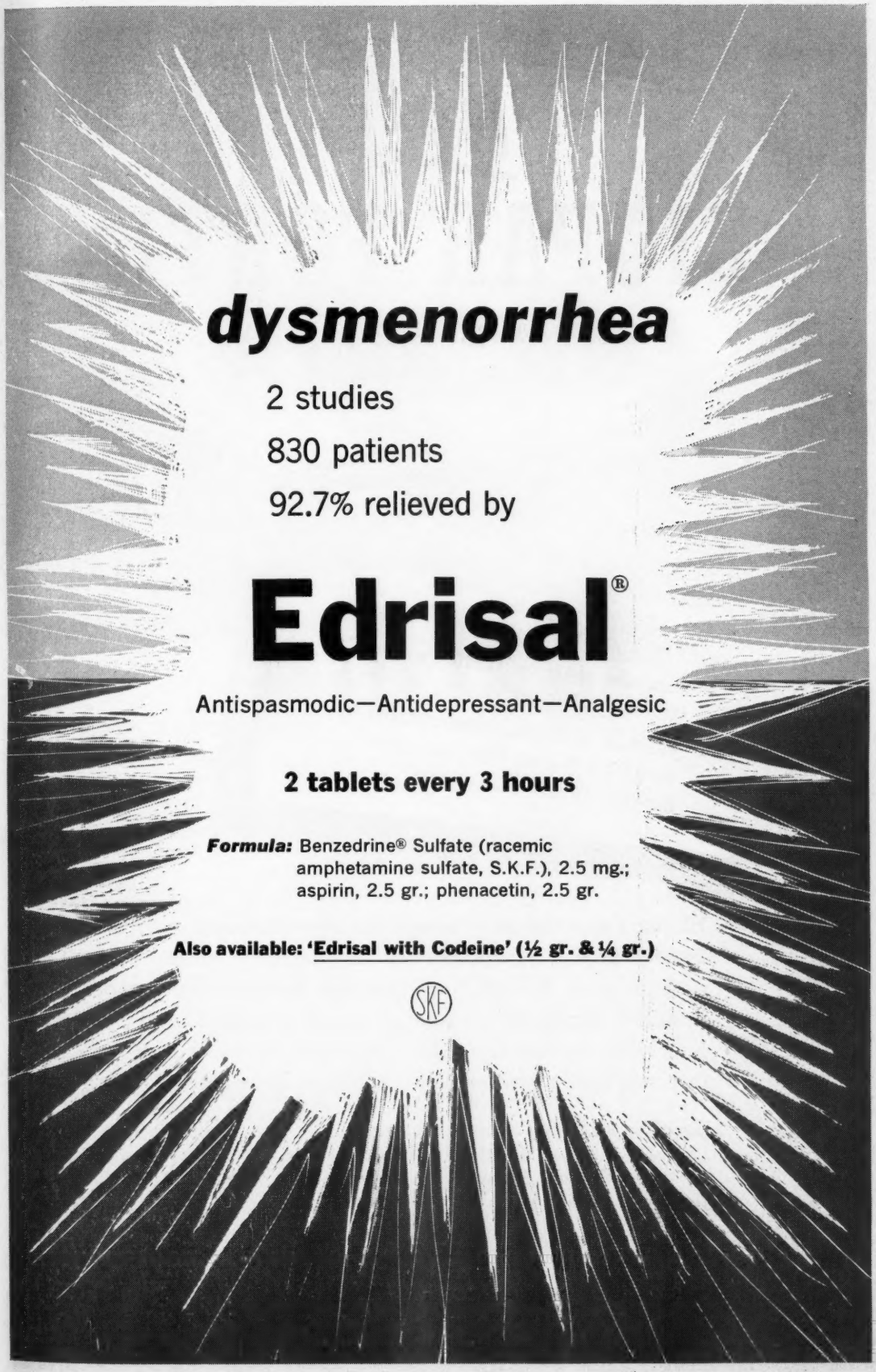
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American Journal of Obstetrics and Gynecology

VOL. 73 MARCH, 1957 NO. 3

Transactions of the Sixty-seventh Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia September 6, 7, and 8, 1956

OUR OBJECTIVES*

Presidential Address

LAWRENCE M. RANDALL, M.D., ROCHESTER, MINN.

(From the Section of Obstetrics and Gynecology, Mayo Clinic and Mayo Foundation†)

ONE of the traditions of societies is the selection of a presiding officer who is permitted, during some meeting in his tenure of office, to give an address on a subject of his own choice. Some 65 presidents of the American Association of Obstetricians and Gynecologists previously have been accorded this privilege. Commonly, each has expressed his appreciation of the honor thus conferred upon him—a sentiment which I now earnestly affirm. Probably each of my predecessors has been concerned by the magnitude of the occasion. To obtain a degree of historical background I reviewed the volumes of our *Transactions,* and I suspect that such an action has been a common preliminary preoccupation of many of my predecessors—preoccupied with the hope that what they may have to say will, in some manner, withstand comparison with what has been said previously. Thus, one searches for a text, so to speak.

The Native Wisdom of Our Forebears

Yet, this scanning of our early records has been rewarding to me, for I found a theme that had been suggested by Ross[1] in 1897. It goes thus: "We are all of us teachers, we speak and we write. We have met again to compare

*Presented at the Sixty-seventh Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Va., Sept. 6 to 8, 1956.

†The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

our notes of another year of work and observation. We, as teachers, are gathered together to teach one another." Ross also nicely phrased one of his own observations: "There are two operations performed that I think are of doubtful value, the fastening of the kidney to the side and the fastening of the uterus anywhere." Another cogent remark which pleased me is that of Parvin,[2] which appears on the third page of the first volume of our *Transactions,* in 1888: "It cannot be denied that there is a growing belief in the professional mind that these operations [laparotomies] are too frequently resorted to, and, therefore, their indications ought to be clearly established, and the presence of the latter conclusively demonstrated before a woman is subjected to what otherwise is an odious mutilation." Shades, perhaps, of the unnecessary hysterectomy well stated 67 years ago.

Every Man a Teacher of Others

These remarks of our medical forebears led me, then, to some thoughts on medical education. I am well aware that medical education is no new subject for a presidential address; indeed, quite recently two of your presidents adverted to such a theme in their addresses. Yet a measure of repetition is justifiable, because there are so many facets to this important problem which is continually confronting us. Actually, the subject itself is so expansive that no one could possibly encompass it within the confines of a short address.

Cosgrove,[3] six years ago, in his presidential address entitled "Our Responsibility," emphasized the need of recognizing the responsibility of each of us to teach those who come after us. What should be given to them, he thought, is an understanding not only of the material things of medicine, but also the great ideals which constitute the throbbing heart of medicine: the ideals of self-sacrifice, of service above and beyond the requisites for pecuniary gain, and the development of a medical and social conscience. These are altruistic objectives with which we must all agree. By extension, Cosgrove's use of the term "material things" caused me to reflect on a subject that has received attention from members of the Council and from individual Fellows: the objectives of this Association. I am not prepared to enumerate possible objectives—indeed a list of them does not exist—but I am confident that everyone would regard the enhancement of medical education as a possible objective of the Association.

Our Association and the Passing Years

Let us first consider what has taken place in this field during the life span of our Association. The birth of this organization (1888) coincides with the first concerted attempt toward graduate medical education in the United States at the Johns Hopkins Hospital, but it was to be many years before this educational experience would become widely propagated. In fact, it might be said that the opposite took place, for in the first decade of this century there was a veritable mushrooming of more than 160 medical schools, many of them proprietary. The massive weight of numbers alone would operate adversely

against the possibility that all of them could be acceptable educational institutions. The Council on Medical Education of the American Medical Association was formed in 1904, and it took cognizance of this unhealthy situation. It was not until the report of Abraham Flexner[4] in 1910, however, that definitive action occurred. There followed in 1914 the first list of medical schools which offered approved internships, and these numbered only three. Thus, the decade 1910 to 1920 marked the establishment of medical education as a university discipline with sharply defined educational standards. However, as late as 1915 the president of a large university bemoaned the fact that success in medical practice as a specialist depended almost entirely upon native ability, rather than upon systematic training. Nevertheless, the first step toward the establishment of standards for special medical practice came about in 1917, when the American Board of Ophthalmology, Inc., began to function. This was followed by the establishment of the American Board of Otolaryngology, Inc., in 1924.

We now come to the year 1925, when the Council on Medical Education and Hospitals of the American Medical Association published the first list, comprised of 27 institutions, which offered approved residences and graduate courses. In 1927 there germinated in this Association the idea that led to the organization and finally the first meeting of the American Board of Obstetrics and Gynecology, Inc., in September of 1930. This was the third of the specialty boards to be created.

The next ten years witnessed a great increase in the emphasis on graduate education. By 1934, 69 institutions offered 240 positions for training in obstetrics or gynecology, or both, among a total of 109 institutions offering 2,203 residency positions in all fields of medicine. These numbers were increased, in 1939, to 518 programs offering 4,562 residency and fellowship positions. Shortly thereafter came the second World War, when the advantages of special training became increasingly obvious to both physicians and patients.

Thus, in the ten years after 1946 there has been a greater demand for graduate education and training in all branches of medicine, including general practice.

The Prospect Before Us

It is interesting to remember that on June 21, 1768, a class of 10 students received the first medical degree conferred in America, from the College of Philadelphia Medical School, now the University of Pennsylvania, and that in 1946, 5,000 physicians were graduated from our medical schools. In the past decade this number has increased to something more than 7,000, or about 30 per cent. At the same time the total number of all positions available for residency training has increased from 8,930 in 1946 to 18,669 in 1950. In 1955, 1,201 institutions afforded 25,841 residency-training positions in 28 branches of medicine. Graduate training in obstetrics and gynecology has kept pace; 470 programs now afford approximately 2,084 positions, compared to 247 programs yielding 669 residency positions in 1946. This disproportionate increase in positions for residency training compared to the increase in numbers of

graduates is the result of many changes. It is probably a logical sequel to the progress in medical knowledge during the past ten years. Nonetheless, the colossus which graduate education has become is of concern to medical educators. That they are disquieted by the problem can be shown by many pronouncements from their midst; I quote a few:

"Clear and well directed thinking was never more important in medical education than it is today."[5]

"Quality of personnel rather than quantity of men and money is the first essential in medical education."[5]

"The student must acquire the learning habit during his period of training. He must be given the opportunity to learn rather than being taught."[6]

"For the teacher two problems exist, education, which is concerned with teaching and study for the purpose of understanding, and training, which has to do with habits and technic."[5]

"One of the problems of medical education is how to make the scholarly attitude persist through life, how to insure that the physician will continue professional, not lapse into merely vocational or commercial."—Means.

"A little reflection is adequate to conclude that there is intense competition for residents even by the better training institutions, that the most effective competitive weapon is an unremitting determination to offer residents a superior educational experience."[7]

"Today's residents will determine the quality and character of medicine tomorrow. Accordingly, the future of medical education will be decided by the public and the leaders of medical schools and universities."[5]

"Research is vitalizing but teaching is vitalizing too. There is overemphasis on research . . . the fact remains that we do not place enough emphasis on teaching."[5]

These are but excerpts from thoughtful and thought-provoking addresses by physicians experienced in medical education at all levels who, while busy with the present, have paused to ponder the future. They present points of view that well could be debated by teachers. The concern they have manifested has resulted in further analyses of educational programs, selection of candidates for undergraduate and graduate medical education and, equally important, selection and training of teachers and evaluation of curricula.

Subjects such as these involve many factors, and the multitudinous problems which arise are not easily mastered. Consider, for example, the large volume of work in the care of patients on a busy medical service, the vastness of current medical literature, the increasing complexities of research and practice, each one of which seriously complicates the matter of graduate education for teacher and student. The difficulty multiplies if one accepts the concept that specialization should proceed from the broad base of medical training and experience. The term "fragmentation" of medical practice is heard and, indeed, the conditions which this term connotes are more or less inevitable, for obvious reasons. That is, owing to the modern demands of the society in which we live some narrowing of medical research and practice must

result, but this contraction should take place against a broad educational background of medical knowledge that ultimately, for the individual, becomes a form of wisdom.

Again, viewed against the perplexities of the current scene, one is impressed with the acumen of members of this Association of 60 years ago. I should like to repeat the following observation of one of our former presidents.[8] It was quoted by Bloss in 1949, but it is sufficiently pertinent now to warrant repetition: "The characteristic of the present era, one that distinguishes it from former civilizations, is that the process of specialization is never carried to the point of complete segmentation. Each specialty, however assiduously cultivated, remains an integral part of the great general profession . . . . All specialists today are primarily the products of general medical culture. The act of specialization takes place after, and not before, entrance into the general profession. When this order is changed, then comes the day of danger."

The word "danger" might well have been applied to conditions in 1896 when, as we have seen, medical education was carried on in something like chaos. At that time basic medical education was sketchy, formal training after graduation scarcely existed, and a physician could easily become a specialist by merely stating that he was one. The housing of many training programs under one roof, as it were, with the possibilities of integration of teaching effort, was scarcely under way. Today concern, interest, and clear and well-directed thinking, rather than "danger," would apply to the efforts being made in this field. More concretely, we may observe that thought today is directed toward attracting the superior candidate for residency training in obstetrics and gynecology, as was emphasized by the report of Gardner[9]; toward attracting superior residents to teaching positions, toward teaching them how to teach, and toward making the positions of teachers attractive and rewarding. While there are extraneous or ancillary factors to this problem, which I presume are the basic concerns of presidents and deans, the burden and responsibility for solution rest upon the shoulders of each one of us, and offer a challenge to all of us.

The Society in Teaching

We have thus far considered teacher and student in relation to medical education. I shall now presume to speculate on the role of the medical society in this important field. First of all, it ought to be plain that medical societies should and do have definite contributions to render to medical education other than those which emanate from their scientific programs. Search of previous programs of this society reveals that on occasion teaching has been discussed; yet, as I review meetings of this and other societies that I have attended during the past 25 years, I am compelled to observe that this subject constitutes a small minority of presentations. Perhaps the impression is generally entertained that the rapprochement of the medical society with medical education is not the concern of medical-society programs, and that it should be left for meetings such as those of the Association of the American Medical Colleges.

With this view I cannot agree. I have the conviction that the responsibility rests more widely than upon organizations devoted primarily to medical education.

Medical societies are born, so to speak, and they also grow up. As they grow, and as civilization and medicine advance, the responsibilities of such societies are inevitably altered. Consider our own Association. When it was formed in 1888, only one other national society was devoted to the specialty which it represents. There were no publications devoted to obstetrics and gynecology. Graduate education hardly existed, postgraduate experience was difficult to secure, medical practice itself was less complicated and travel was a thing of considerable moment. The meetings of this organization offered the one annual opportunity for an obstetrician and gynecologist to mingle with a large group of his confreres for what was essentially an educational experience. This Association has continued to afford such an opportunity in the form of the annual meeting and the excellent mid-year clinics. We may be reminded that the first mid-year clinic was held in Columbus, Ohio, on March 11, 1929.

Remember, however, that for many years only three meetings* of national scope related to obstetrics and gynecology were held annually, and that therefore a relatively small percentage of physicians with an interest in this specialty could avail themselves of such a privilege. This situation has been related to the phases of the development of specialty practice which I have mentioned. It is significant, then, that regional obstetric and gynecologic societies such as the Central, New England, Pacific Coast, and South Atlantic appeared about the third decade of this century, coincident with the growth and development of graduate training. This has been followed by a tremendous increase in the number of meetings devoted to obstetrics and gynecology, all offering an educational experience. The first of the six American Congresses held in 1938 is an example. After World War II plans began which eventuated in the formation of the American Academy, now the American College, of Obstetricians and Gynecologists, which has asserted itself on the national scene.

We have, then, several national obstetric and gynecologic societies and a number of regional organizations where obstetricians and gynecologists gather to discuss research and practice, but rarely the problems of medical education as related to training and teaching those who are to follow us. I would observe that medical education of this nature is a fruitful field of endeavor with many material benefits, but that the societies themselves pay little mind to it. What is perhaps equally important, medical societies in general do not integrate their efforts when they do give some heed to the problems of medical education.

*The Section on Obstetrics and Diseases of Women and Children of the American Medical Association was created in 1873. In 1880 the words "and Children" were dropped from the title. At the annual meeting of the American Medical Association in 1911 the title of the section was changed to Section on Obstetrics and Gynecology; in 1912 it became the Section on Obstetrics, Gynecology and Abdominal Surgery, and in 1938 it became known once again as the Section on Obstetrics and Gynecology.

The Current Scene

This brief résumé of the development of medical education and the history of our Association rather returns one to the subject of the functions and objectives of the American Association of Obstetricians and Gynecologists today. We have seen that in the early days the objectives concerned an educational experience in the meetings that could be secured by no other means. The Association in fact was conceived as existing for the benefit of the members themselves in the form of an educational experience. Yet, as the years passed, it was evident that members were giving some consideration to the status of specialty in relation to medicine as a whole. They emphasized the desirability, perhaps the necessity, of broad experience, at that time exemplified by the general practice of medicine, if you will, as a background against, or a basis upon which, the practice of a specialty should be erected.

Intimations of the Future

It is very difficult for us in 1956 to grasp the spirit and the setting of medical meetings of more than a half-century ago. Yet, careful scrutiny of our own *Transactions* inevitably leaves the impression that these pioneers were vitally interested in and aware of the problems of their day. Are we of today as equally aware of our own? Currently there is a plethora of meetings. All of us belong to many societies; we attend several meetings a year which are concerned primarily with research and practice, but not often with education and the future of medicine. National medical societies are made up of leaders in the profession. Do national societies themselves function as leaders? Certainly the general notion is that they do, but we may well reflect on whether this is actually true. I grant that attendance at our annual meetings and mid-year clinics to me is an educational experience of great worth, but are we contributing, in an era of intense medical competition, as much as would be expected of an old and venerable organization entrusted with uncommon responsibility?

We have labored diligently, and I think wisely, to attract the best of our specialty to membership in the Association. Yet are we, a group of individuals of professional attainment, doing all that can be done toward the salutary shaping of the medical future? This subject was last discussed in the Council meeting of September, 1955. It was moved that consideration of this matter be continued to the point of specific recommendation. I would urge that this course be pursued. And when attention is given to matters of the future, it seems to me that more active participation in the problems of graduate medical education may rightfully be regarded as an objective of a society the members of which, with few exceptions, are of professorial rank.

There must be other objectives, perhaps of more importance, and it is to be hoped that the mention of this one will stimulate thought concerning them. I do not imply that we have not had objectives in the past. The Chorionepithelioma Registry and the planning and work that led to the establishment

of the American Board of Obstetrics and Gynecology, Inc., are two examples of achievement from which we may derive great satisfactions. I do imply, however, that future objectives should be of concern to the Fellowship.

I have been a Fellow of this Association for 25 years, and I have counted this membership a privilege. I must own, I fear, that I have gained from it much more than I have contributed. Yet I can discern clearly that we dwell in an atmosphere of spirited competition and swift-paced advancement. Against the framework of such a variegated and sometimes confusing scene I am jealous of the position of the American Association of Obstetricians and Gynecologists, and I wish it to be ever thoughtful of activities and objectives which wise men can envisage, as well as those which we can perceive now.

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THE USE OF OBSTETRICAL ANALGESIA AT THE MATERNITY HOSPITAL OF GENEVA*

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IN ALL times it has been the task of the physician not only to cure a disease but also to relieve as much as possible the pains of his patients. The recent progress in the field of analgesia and anesthesia has certainly contributed to the fact that medicine has become one of the most popular and considered sciences. In this evolution your country has played an important role and I quote here as an example the discovery of general anesthesia with ether by Morton in 1846 and the early recognition of anesthesiology as a specific branch of medicine. Your country has also been one of the first to admit the right of the expectant mother to relief of pain during childbirth. Notwithstanding the symbolic words in the *Holy Bible:* ". . . in sorrow shalt thou bring forth children . . ." (Genesis, chapter 3, verse 16), Pope Pius XII[26] has recently approved methods which permit relieving the pains of labor provided no interference with the normal evolution of delivery occurs and no danger for the mother or the child is created.

There are obstetricians who think that only degenerated and overcivilized women with abnormal sensitivity will ask for obstetrical analgesia. It is true that intellectual development enhances in general the sensitivity and that primitive people are frequently better trained to suffer pains. Many observers and explorers have, however, reported that labor pains do occur also in less civilized countries and in savage tribes with "natural" living.

In France one says: "On a toujours assez de courage pour supporter les douleurs d'autrui." That is, "One has easily enough courage to bear the pain of others." It seems to me, however, that there is no merit in an obstetrician's showing sufficient courage to endure the pains of his patients. The fight against suffering during childbirth is a normal task of the physician not only as an act of humanity but also for definite medical reasons. Women may avoid a new pregnancy merely out of fear of a recurrence of the sharp pains they felt during a prior delivery. In other cases the psychic trauma caused by the pain of labor may disturb later on the establishment of a normal mother-child relationship. Finally, excessive pains may accelerate the exhaustion of the parturient and contribute to secondary uterine inertia, and the restlessness of the desperate patient may impair the correct nursing care and the necessary asepsis.

For these reasons we practice at the Maternity Hospital in Geneva, in a fair percentage of cases, various methods of obstetrical analgesia as Table I shows.

*The Joseph Price Oration, presented at the Sixty-seventh Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Va., Sept. 6 to 8, 1956.

TABLE I. METHODS OF OBSTETRICAL ANALGESIA USED IN THE MATERNITY HOSPITAL AT GENEVA

YEAR	1950		1951		1952		1953		1954		1955		1956 (TO JUNE 30)	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Total number of deliveries	1,410		1,406		1,380		1,497		1,534		1,702		922	
Deliveries under Trilene and nitrous oxide	326	23	591	42	726	52	840	56	608	39	170	10	59	6.4
Delivery under pudendal blocks	63	4.4	48	3.4	40	2.9	39	2.5	52	3.4	49	2.9	29	3.1
Delivery under saddle blocks	81	5.7	72	5.1	35	2.5	2	0.1	—		—		—	
Delivery under continuous lumbar peridural analgesia	17	1.2	16	1.1	88	6.4	152	10	106	6.9	108	6.3	48	5.2
Delivery by psychoprophylactic preparation for painless childbirth	—		—		—		—		3		454		250	27
									26.5% of all deliveries					

Most of these methods are well known and widely used in your country and I will therefore restrict myself to mentioning later on in my lecture which place these techniques occupy at present in our own therapy.

In the past five years I have had the opportunity of attending during their confinement a small group of patients who had undergone throughout their pregnancy a thorough training in special gymnastics according to the method of Margaret Morris[18] and inspired by the ideas of Grantly Dick Read.[4-8] The relief of pain obtained by this type of preparation seemed not entirely convincing to me. On the other hand, I have been very much impressed by the behavior of a few parturients who had followed a course of psychoprophylactic preparation for painless childbirth according to the method applied by Lamaze in Paris.

This method, which was first developed by Nikolaiev[19-21] in Russia, was explained by Lamaze[13] in a lecture given in Geneva. In this report the method seemed based on sound and rather simple principles and its application appeared not only innocuous but even advantageous from a general obstetrical point of view by involving a more continuous and watchful attendance on the parturient. Geisendorf,[11] a colleague and co-worker of mine, studied the technique of psychoprophylactic preparation for painless childbirth during a stay at the "Clinique des métallurgistes" in Paris, and he confirmed fully the enthusiastic reports of others on the excellent results obtained by Lamaze.

I asked Geisendorf two years ago to introduce the psychoprophylactic method in my Department and, though still under investigation, this technique has already proved to be of great theoretical and practical interest and we consider our first results very encouraging.

I therefore thought that our experience with this type of obstetrical analgesia, even if limited at the present time, might well be a stimulating subject for a lecture before an audience of obstetricians, whose interest in the fight against pain during childbirth and whose high competence in this field are well known to me.

My intention is to outline first the underlying principles of the method and the technique of its application, then to report and to discuss our own results. Finally, I would like to draw some general conclusions from our experience and that of other authors with this particular method for easing childbirth which is more and more used in France, the French-speaking part of Switzerland, Belgium, Italy, Spain, Portugal, Argentina, and many other countries.

The Theory and Techniques of Psychoprophylactic Preparation for Childbirth

Psychoprophylactic preparation for painless childbirth is based on Pavlov's[23, 24] concept of pain perception and his theory of conditioned reflexes. According to Pavlov, the perception of pain is localized in the cerebral cortex. The activation of this center, like that of any other cortical zone, produces in its surroundings an area of inhibition, thus limiting the stimulus to a certain

part of the cortex. When several cortical areas are activated simultaneously the predominant stimulus may diminish or even inhibit the activity of the other stimulated brain centers.

Unconditioned or fundamental reflexes are inborn and provoke stereotyped reactions, as, for instance, in the newborn sucking is a response to a contact of the lips and the tongue.

Conditioned reflexes, on the other hand, are reactions which result from a newly established, temporary link between certain cerebral centers as demonstrated by the classical experiment of Pavlov in the dog. In this animal the view of food provokes an abundant salivation. If the presentation of food to the dog is associated repeatedly with the ringing of a bell, this latter stimulus alone will finally become sufficient to induce the secretion of the salivary glands.

Rogov[28] has shown in a spectacular experiment that in human beings conditioned reflexes may be as easily created by words which evoke certain ideas as by other stimuli like optical, acoustical, or sensory signals.

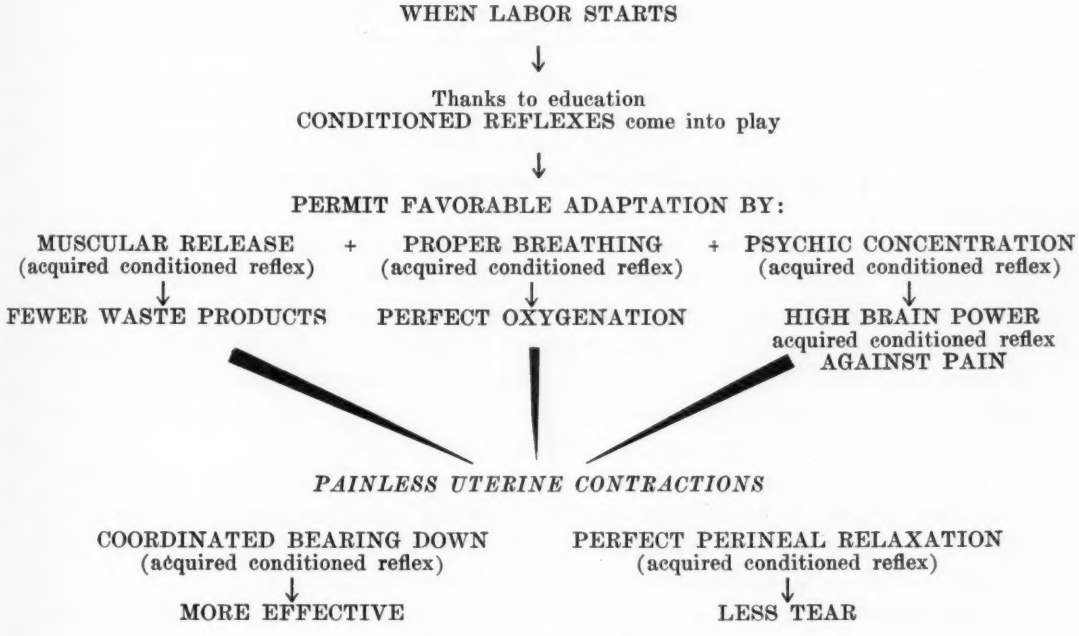
The sensation of pain which normally provokes a defense reaction and an unpleasant feeling may, by the mechanism of conditioned reflexes, become linked to a strong activity of other brain centers than that of pain perception. Thus, the unpleasant feeling of pain will be covered by other sensations and the defense reflex replaced by another reaction. Anxiety and psychic tension, on the other hand, will, in general, increase the feeling of pain. In the woman the perception of uterine contractions is linked beyond a certain intensity threshold with a feeling of suffering and provokes a status of anxiety. The traditional belief that pain and danger are necessarily connected with childbirth increases this reaction. Talk about the horror of confinement, erroneous sex education, or particular subconscious psychological features of the patient may furthermore contribute to the fact that uterine contractions during normal labor or even during menstruation are often felt as a sharp and unbearable pain.

The aim of psychoprophylactic preparation for easing childbirth is to replace the negative reflexes generally established in connection with the perception of uterine contractions and that of distention of the pelvic floor by newly created positive conditioned reflexes. The method tries, furthermore, to diminish or abolish the perception of pain during labor by an intense stimulation of psychomotor brain centers. To reach this goal the expectant mother is submitted to a specific psychic and physical training.

First of all, the expectant mother is informed of the principle of the method and the program of training. A simple orientation on the physiology of pregnancy and labor familiarizes her then with the phenomena which will occur during childbirth. This knowledge helps to remove a great deal of her anxiety and tension when faced with an unknown and dreaded experience. During the preparation the patient is repeatedly taught that the normal contractions of the uterus may just as well be painless as those of other muscles like the bowel or the bladder, and that the parturient may largely contribute

to this by a continuous active participation during labor. An attempt is thus made to break down the classical dogma that childbirth must be painful. All the sensations the future parturient will feel during delivery are described to her as normal physiological signs of the progress of labor, which brings her nearer to the happy birth of her baby. The patient is told how to react to these sensations by concentrating on complete relaxation, on appropriate breathing, and finally on a special technique of pushing in order to favor the progress of labor and to abolish the feeling of pain.

TABLE II. THEORETICAL CONDITION OF THE WELL-PREPARED MOTHERS



The women are prepared by specific exercises for this voluntary muscular relaxation, for the particular type of fast and shallow breathing, and for the pushing down without contraction of the pelvic floor. The expectant mothers have to practice these exercises at home daily for a few minutes and it is desirable that the husband assume the supervision of some part of this preparation, thus becoming an interested and cooperative partner. In this program relaxation is not meant as a passive and stoic state of mind, but as an active effort which stimulates cortical centers and therefore masks the pain perception. The special type of breathing acts in a similar way as a conditioned reflex, released by the perception of a beginning uterine contraction and linked with a strong positive psychic reaction, namely, the evocation of the happy event of a normal childbirth without pain (Table II).

The mentioned physical and psychic training is taught in Paris in eight lectures, whereas we have limited it, in Geneva, to seven lectures, omitting the one devoted to the description of the physiology of the brain and the principle of the conditioned reflex. The lectures take place in the hospital regularly once a week from the thirtieth to the thirty-seventh week of pregnancy, and are given to groups of 5 to 8 women. If a pregnant woman has not been delivered within two weeks after the last lecture, she has to follow a refresher course of one hour.

In our hospital two psychologists who have studied the method in Paris are entrusted with the preparation of our patients. The lectures on the anatomy of the genital organs and on the physiology of delivery, however, are read by obstetricians, and thus the future parturients can establish a first contact with members of the obstetrical staff who will, later on, take care of them during their delivery. Whatever the professional background of the monitor may be, he should have not only a good knowledge of obstetrics and psychology, but also a didactic talent, and should be a good persuasive speaker.

We have adopted the following program for our seven lectures: The first lecture introduces the method by explaining in a very simple way its basic principle; the anatomy of the female genital organs is then reviewed and the importance of three main points is stressed: (1) the necessity of performing the conditioning exercises regularly; (2) asking questions on each point which is not fully understood; and (3) paying no attention whatsoever to any hearsay tales of the pain and difficulty of childbirth.

The second lecture deals with the physiology of respiration and appropriate techniques of breathing, these techniques being necessary for optimal oxygenation which is a condition of painless muscular contractions. The expectant mother is made conscious of her respiratory muscles.

The third lecture is devoted to neuromuscular education. The group learns that general relaxation during labor will save energy and oxygen in favor of the contracting uterus; exercises for progressive muscular relaxation extending from one limb to the whole body are demonstrated. The pregnant women then have to practice these exercises twice a day at home for a few minutes.

The fourth lecture gives, after a short survey of the physiology of pregnancy, a thorough description of the different stages of labor. The participants learn to perceive the painless Braxton Hicks contractions.

In the fifth lecture, the future parturients are taught how to behave during the first stage of labor. At the onset of labor the patient concentrates only on relaxation; from 1 to 4 cm. of dilatation she must, furthermore, breathe deeply and slowly during contractions; when the dilatation has reached 5 cm., shallow and fast breathing is started (Fig. 1). After this lecture the two types of breathing become part of the daily training. If the pregnant women practice the breathing exercises repeatedly at the moment of Braxton Hicks contractions, a conditioned reflex will be created, linking the specific type of breathing with the perception of uterine contractions which are painless.

In the sixth lecture the expectant mothers learn how to behave during the second stage of labor. A special technique of bearing down without contraction of the muscles of the pelvic floor is demonstrated and built up as a conditioned reflex to verbal signals. When the head is crowning the bearing down must at once be replaced by fast and shallow breathing. This sudden change is also included in the daily exercises.

The seventh lecture gives a general repetition; the theory is reviewed and the exercises are separately checked in each patient. Mothers who have been delivered recently are introduced to the group and asked to report on their experience with psychoprophylactic preparation. The signs of the onset of labor are recalled.

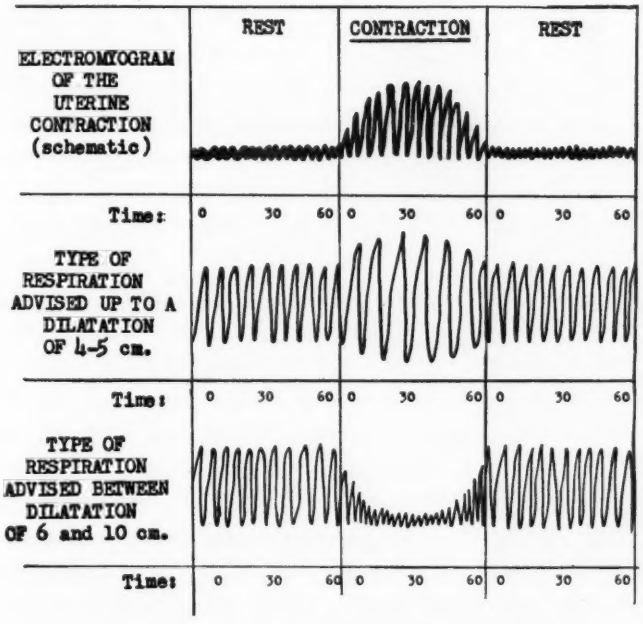

REST
CONTRACTION
REST
ELECTROMYOGRAM OF THE UTERINE CONTRACTION (schematic)
Time:
0 30 60 0 30 60 0 30 60
TYPE OF RESPIRATION ADVISED UP TO A DILATATION OF 4-5 cm.
Time:
0 30 60 0 30 60 0 30 60
TYPE OF RESPIRATION ADVISED BETWEEN DILATATION OF 6 and 10 cm.
Time:
0 30 60 0 30 60 0 30 60

Fig. 1.—Type of respiration during dilatation.

In addition to this teaching program, we show to a larger group of pregnant women a moving picture* which recalls the basis of the method and the practical exercises and, finally, shows several examples of painless childbirth. The moving picture is commented on by a member of the nursing staff and followed by a free discussion. Husbands are admitted to this meeting with the hope that they may later on become valuable allies during the delivery of their wives.

To obtain good results by the method, its correct application during delivery is as important as a good preparation during pregnancy. Immediately after the arrival of the parturient at the hospital and after the first obstetrical examination, a rehearsal is held. This procedure serves to establish a good personal contact between the patient and the attending midwife or physician and helps to make her feel self-confident and trustful toward the nursing

*Provided by the courtesy of Dr. Lamaze, Paris.

staff. In normal cases it is useful to keep the parturients, until a dilatation of about 4 cm. is reached, in a kind of entertainment lobby. In this cozy room, the expectant mothers will remain together under supervision of a nurse, with games, illustrated newspapers, radio and television. These distractions will help them not to pay too much attention to the uterine contractions. Once in bed, the parturient must be put in the most comfortable position with foam rubber pillows at the back and bolsters under the knees. As soon as dilatation is advanced further than 5 to 6 cm. individual coaching becomes indispensable and a cooperative husband may be helpful at this stage of labor. The most difficult period of labor is generally when dilatation passes from 7 to 9 cm. At this time we administer oxygen liberally in high concentrations for three main reasons: (1) its stimulating effect which contributes to a feeling of well-being; (2) its analgesic effect which has been demonstrated by the papers of various authors[10, 22, 25, 29, 30]; and (3) the beneficial psychic influence which the use of this therapeutic procedure exerts. Eastman[9] and others[31] have furthermore stressed the value of oxygen administration for the prevention of intrauterine anoxia of the fetus. During the second stage of labor the conditioned reflex of bearing down must be set in motion by precise and stereotyped orders.

Exhaustion, sleep, and thirst disable the patient who can no longer maintain the intense brain activity and voluntary effort which are necessary for the success of the method. During the first stage of labor the parturient gets upon request frequent sips of ice water and during the whole labor we are quite liberal with intravenous injections of glucose, possibly combined with Coramine and/or vitamins. The conditioning which results from psychoprophylactic preparation is unstable and must be strengthened on each occasion during the delivery, first by means of the mentioned exercises for breathing and relaxation and also by words of encouragement. All factors which could disturb the conditioning must be carefully avoided, as for instance painful rectal examinations or large enemas. In the presence of the patient one should never use unsuitable terms which evoke pain, suffering, or danger, but the patient should be informed at regular intervals of the progress of her labor.

My survey of the method of psychoprophylactic preparation for painless childbirth has perforce been incomplete and has perhaps unduly simplified a very complex matter. I therefore refer those of you who want further theoretical and practical details to the book which will be published in English by my co-worker, Bonstein,[1] and to the original French literature on the subject.[12-17, 27, 35] Much of what I have said will be familiar to those who know the pioneer work of Read[4-8] and of Thoms.[32-34] The psychoprophylactic method and natural childbirth without fear as practiced by Read or by Thoms have in fact the following three points in common: (1) Fear enhances the perception of pain but may diminish or disappear when the parturient knows about the physiology of labor. (2) Psychic tension enhances the perception of pain but the parturient may more easily relax if childbirth takes place in

a calm and agreeable atmosphere and when good human contacts are established between her and the nursing personnel. (3) Muscular relaxation and a specific type of breathing diminish or abolish the pain of labor.

There is no fundamental difference between the two methods. Many of Read's followers, however, attribute the main importance to the correct preparation of the muscles by physical training. They believe that intense gymnastics during pregnancy and muscular relaxation with appropriate breathing during childbirth can modify the type of uterine contractions, thus diminishing the pain. In the psychoprophylactic method the physical training serves mainly to modify the cerebral activities by creating new conditioned reflexes. According to latter concept, relaxation and breathing are not used in order to modify the pattern of uterine activity but to decrease the perception of pain in the cerebral cortex. Read casts the parturient in a passive role during childbirth, and relaxation should help her to become less conscious. With the psychoprophylactic method, on the contrary, the parturient is exhorted to a maximal psychic and physical activity and she is asked to perform her childbirth like a personal achievement.

In a recent conversation which I had with Grantly Dick Read his concept proved to be very similar to the ideas expressed in my lecture. It is not my intention to start an argument on the priority and interrelation of both methods. Neither am I concerned with the geographical or political background of a therapeutic technique, since I think that we, medical men, should investigate objectively for the benefit of our patients any new method which appears to be of interest.

I have no experience with Thoms' method and very little with Read's and I am not qualified to make a statement on their value in comparison with psychoprophylactic preparation. Nevertheless, I would like to stress two advantages of the latter method: The preparation starts only in the thirtieth week of pregnancy, the teaching takes only seven to eight hours, and the practical exercises a few minutes every day. The exercises need no physical effort and are not harmful even in cases of threatened premature labor or other disturbances of pregnancy, where gymnastics would be dangerous.

It is obvious that the psychoprophylactic preparation evokes the role of suggestion and its action has frequently been ascribed to hypnotism. There is, however, an essential difference: In hypnotism the patient is in a cataleptic or lethargic state, whereas the parturient with psychoprophylactic preparation must be fully conscious and intellectually active. No dangerous emotional interdependence is established between the monitor and the patient, her personality is not disconnected, and the subconscious mind is not affected as in hypnotism.

I am well aware of the fact that the explanation for the mechanism by which psychoprophylactic preparation works may be subject to criticism. Being neither a physiologist, nor a psychologist, I do not intend to theorize further on this subject, but would like to report the results obtained by the practice of the method.

Results Obtained in a Program of Psychoprophylactic Preparation for Childbirth

From December, 1954, to the end of June, 1956, we observed in the Maternity Hospital at Geneva 707 confinements of women who had undergone a psychoprophylactic preparation for easing childbirth. This figure represents 27 per cent of the total number of deliveries in the hospital during the same period of time. The fact that only a minority of our patients followed the preparatory course is caused by differing circumstances: Lack of time for women busy with professions or housework, lack of transportation facilities for people living far away from the place where the lectures were given; lack of knowledge of French, the language of teaching, by German- or Italian-speaking patients, and lack of interest in the method in expectant mothers whose former deliveries had been easy. At present, we notice, however, a slow but constant rise in the percentage of women who undergo psychoprophylactic preparation and we attribute this rise to the advertising activity of the women who have been satisfied with the method.

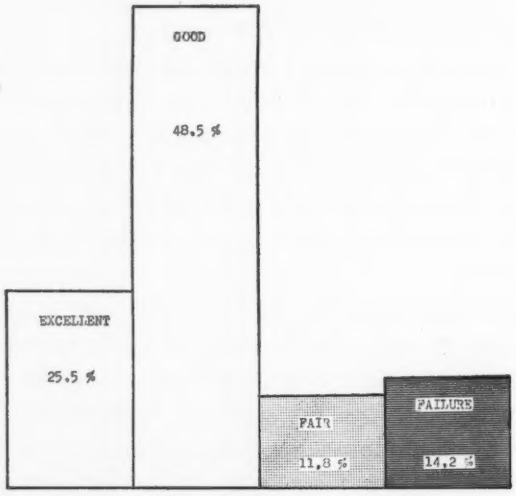


Fig. 2.—Evaluation of the results of psychoprophylactic preparation in 707 confinements at the Maternity Hospital at Geneva.

In our whole series of 707 cases we considered the result as excellent in 25 per cent of the parturients and as good in 50 per cent of them. In 11 per cent of cases the success was only moderate as the patients complained of pains at one or the other stage of labor. Failure was complete in 14 per cent, where the patients complained of severe pains, so that we were frequently obliged to use another method of obstetrical analgesia (Fig. 2). Our figures are slightly below those published by Lamaze for 4,847 deliveries in the "Clinique des métallurgistes" at Paris (Table III). Nevertheless, our results seem surprisingly good if we consider that we started the method under quite unfavorable conditions. In the beginning, we had no adequate delivery rooms, so that many patients were disturbed by the screaming of unprepared women. The personnel was not numerous enough to secure good individual coaching and some members of the staff had not had the opportunity of proper training and were therefore skeptical and reluctant.

TABLE III. RESULTS OBTAINED BY DR. LAMAZE IN PARIS (UNTIL OCT. 31, 1955)

DEGREE	NO. OF PATIENTS	PERCENTAGE	TOTAL %
Excellent	893	18.43	
Very good	1,097	22.63	
Good	1,172	24.17	
Fair	859	17.73	82.96
Tolerable	595	12.28	
Failures	231	4.76	17.04
Total	4,847	100.0	100.0

It may be argued that the intensity of pain has not been registered by precise methods, which unfortunately are still lacking. We must admit that those who evaluate the degree of suffering during labor, patients as well as members of the staff, may be prejudiced by various factors for or against the method. We know by experience how difficult it is to classify complex, subjective impressions in delimited groups.

A considerable effort has been made, however, to come to an objective and correct judgment by proceeding in the following way: The classification of the results was based on well-defined objective and subjective criteria which are shown in Table IV. The final statement is a synthesis of all the observations made by different attendants at various stages of the labor and of the appraisal by the patient herself after the delivery. In controversial cases the less optimistic interpretation prevails. For questioning the patients on their impressions, stereotyped sentences are used immediately after delivery and again seven days later by two different persons.

TABLE IV. CRITERIA FOR THE CLASSIFICATION OF RESULTS

CLASS	APPRAISAL BY PARTURIENT	APPRAISAL BY PHYSICIAN AND/OR MIDWIFE
Excellent	No feeling of pain	Patient relaxed, calm with perfect self-control, no complaints, smiles
Good	Occasional slight pain, perfectly tolerable, no need for analgesia	No complaints but some temporary tension alleviated by massaging
Fair	Perception of disturbing pain, desire for some analgesia	Complaints, some restlessness, occasional moaning, but response to orders and encouragements
Failure	Intolerable pain	Screaming, restlessness, psychomotor excitation, no response to orders and encouragements

Many patients behave quite differently during the first stage, the second stage, and the delivery of the head, and in such cases we found it difficult to make a correct over-all statement on the efficiency of the method. We have, therefore, recently introduced a separate evaluation of the result for the different stages and a small series of patients has been checked with particular care in this manner by my colleague Roux. Fig. 3 shows that failures were infrequent in each one of the three stages. This has been noted in the estimation by the patient herself as well as in the evaluation by the attending staff members. According to the patients' own statements, dilatation was absolutely painless in only a small group, but a high percentage of parturients felt no pain whatever during the second stage and the delivery of the head. If we add the excellent and the good results, we find that stage one was quite satisfactory for three-fourths of the women, and stage two or delivery of the

head even for 90 per cent of them. We were interested to know what the corresponding figures would be in a group of unprepared parturients, who had been delivered during the same period of time and under similar conditions and who had to answer the same questions as the patients with psychoprophylactic preparation. Table V shows that some women may have a painless childbirth even without any special preparation, but this is much less frequent than in patients who have been conditioned during pregnancy. The difference is already significant for stage one, but much more marked for stage two and the delivery of the head. The percentage of excellent and good results together is again higher in the group of prepared women and the difference is most impressive for the stage of delivery (Table VII).

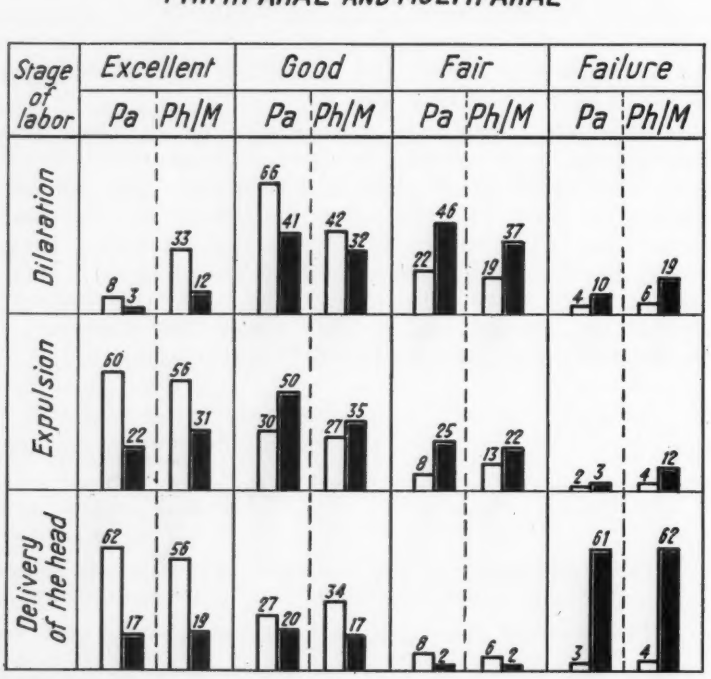


Fig. 3.—Appraisal of the course of delivery in women (primiparas and multiparas) with and without psychoprophylactic preparation (PPP): 92 cases with and 59 without PPP.

For each stage of labor, the height of the columns and the figures indicate the percentage of cases with PPP (white columns) or without PPP (black columns) falling within the respective class of appraisal when the latter has been done either by the parturients themselves (columns headed *Pa*), or by the physician and/or midwife (columns headed *Ph/M*).

Table VI gives the ratio between prepared and unprepared patients for each section of our table and shows clearly the value of the psychoprophylactic method for the alleviation of pain during childbirth. There are, however, two points, which I would like to stress here: Up to now, only 25 per cent of patients reached the goal of a completely painless childbirth after having undergone psychoprophylactic preparation. On the other hand, we observed an appreciable percentage of unprepared women who found the pains of labor quite tolerable and did not need obstetrical analgesia. This latter finding may be due partly to the fact that all parturients, even those who did not follow the lectures for psychoprophylactic preparation, are now taking advantage of the method. They all get oxygen in high concentrations and glucose injections, they are all taught during labor to breathe correctly, and they all benefit from a more comprehensive and watchful attitude of the nurses, midwives, and obstetricians.

TABLE V. BEHAVIOR OF PARTURIENTS IN 59 CASES WITHOUT PSYCHOPROPHYLACTIC PREPARATION

STAGE OF LABOR	EXCELLENT (%)		GOOD (%)		FAIR (%)		FAILURE (%)	
	APPRAISAL BY PARTURIENT	APPRAISAL BY PHYSICIAN AND/OR MIDWIFE	APPRAISAL BY PARTURIENT	APPRAISAL BY PHYSICIAN AND/OR MIDWIFE	APPRAISAL BY PARTURIENT	APPRAISAL BY PHYSICIAN AND/OR MIDWIFE	APPRAISAL BY PARTURIENT	APPRAISAL BY PHYSICIAN AND/OR MIDWIFE
Dilatation	3	12	41	32	46	37	10	19
Expulsion	22	31	50	35	25	22	3	12
Delivery of head	17	19	20	17	2	1.7	61	62.3

TABLE VI. RATIO OF WOMEN WITH PSYCHOPROPHYLACTIC PREPARATION TO WOMEN WITHOUT PSYCHOPROPHYLACTIC PREPARATION IN DIFFERENT CLASSES OF APPRAISAL

STAGE OF LABOR	> 1 = SUCCESS OF THE METHOD				< 1 = SUCCESS OF THE METHOD			
	EXCELLENT (%)		GOOD (%)		FAIR (%)		FAILURE (%)	
	APPRAISAL BY PARTURIENT	APPRAISAL BY PHYSICIAN AND/OR MIDWIFE	APPRAISAL BY PARTURIENT	APPRAISAL BY PHYSICIAN AND/OR MIDWIFE	APPRAISAL BY PARTURIENT	APPRAISAL BY PHYSICIAN AND/OR MIDWIFE	APPRAISAL BY PARTURIENT	APPRAISAL BY PHYSICIAN AND/OR MIDWIFE
Dilatation	2.7	2.7	1.6	1.3	0.43	0.5	0.4	0.32
Expulsion	2.7	1.8	0.6	0.8	0.33	0.6	0.55	0.33
Delivery of head	3.6	2.9	1.35	2.0	4.0	3.5	0.5	0.064

TABLE VII. PERCENTAGE OF PATIENTS WITH EXCELLENT AND GOOD DELIVERIES (Class I + II)

STAGE OF LABOR	RATIO PPP* : NO PPP*	
	PRIMIPARAS	MULTIPARAS
Dilatation	2.3	1.6
Expulsion	1.0	1.4
Delivery of head	1.7	3.3

*PPP = psychoprophylactic preparation.

It is a general opinion that the value of methods for obstetrical analgesia should be checked only in primiparas, as most multiparas have easy deliveries without special procedures. We compared therefore the behavior of prepared and unprepared parturients, separately, for the group of primiparas and multiparas. Figs. 4 and 5 show the results of this study. Among the conditioned patients the percentage of primiparas was almost twice as high as in the group without preparation. Easy deliveries were certainly much more frequent not only in primiparas but also in multiparas who had been conditioned by psychoprophylactic preparation. In primiparas the difference between prepared and unprepared patients was most impressive in the first stage, whereas multiparas showed the greatest benefit by the method during delivery of the head. None of the 36 conditioned multiparas considered stage one as a failure and 11 felt no pain at all. In the group of 38 unconditioned multiparas, on the other hand, only 5 evaluated stage one as excellent and 10 found it extremely painful. None of the unconditioned primiparas had an excellent dilatation and failures were twice as frequent as in prepared primiparas. In both primiparas and multiparas, psychoprophylactic preparation reduces to one tenth the frequency of failures during delivery of the head. The improved behavior of conditioned parturients during this last stage of labor

is of particular value for the breech extraction by the Bracht maneuver. The conscious patient is bearing down vigorously and the abolition of pain permits her to relax the pelvic floor.

When comparing the subjective appraisal by the parturient and the objective evaluation by the physician or midwife (Table VIII), we were surprised to find them identical in a large majority of patients with or without psychoprophylactic preparation. The discrepancies were more frequent with regard to stage one than for the other stages of labor, and in one fourth to one third of these cases it was the statement of the attending personnel which was too optimistic. In the cases where the discrepancy concerned the appraisal of the expulsion or delivery, it was, on the contrary, the impression of the parturient which in general was more favorable. This means that women who appear quite calm during delivery may, nevertheless, feel disturbing pain, whereas parturients who show some excitement and even signs of suffering during expulsion and delivery may afterward be quite satisfied with their confinement. The active cooperation of the parturient during the last stages of labor requires an intense physical and psychic activity. We attribute the more favorable appraisal of expulsion and delivery by the patient to the great influence of such an intense activity on the perception and appraisal of pain.

TABLE VIII. APPRAISAL BY THE PARTURIENT HERSELF AND EVALUATION BY PHYSICIAN AND/OR MIDWIFE
Subjective Statement as Compared to Objective Evaluation

	% BETTER		% THE SAME		% WORSE	
	PPP*	NO PPP	PPP	NO PPP	PPP	NO PPP
Dilatation	11	24	56	52	33	24
Expulsion	23	34	72	47	5	19
Delivery of head	24	20	67	80	9	0

*PPP = psychoprophylactic preparation.

When comparing the statement of the patient immediately after delivery and seven days later (Table IX), we observed that less than half of the unconditioned women maintained their first judgment. Nearly as many of them had after one week a worse impression of their childbirth. In the group of conditioned women, on the other hand, almost 75 per cent of the patients did not change their appraisal. The final statement of the other mothers concerning their delivery was more frequently improved than depreciated after one week.

TABLE IX. APPRAISAL BY THE PATIENT IMMEDIATELY AFTER DELIVERY AND ONE WEEK LATER
Statement After One Week as Compared to Evaluation Immediately After Delivery

	% BETTER		% THE SAME		% WORSE	
	PPP*	NO PPP	PPP	NO PPP	PPP	NO PPP
Dilatation	15	8.5	72	49	13	42.5
Expulsion	19	4.3	71	49	10	46.7
Delivery of head	19	4.8	71	43	10	52.2

*PPP = psychoprophylactic preparation.

When registering in hours the duration of stage one and stage two in all cases, we found similar binomial curves in the group of prepared and unprepared women, thus psychoprophylactic preparation had no influence on the duration of labor in our material.

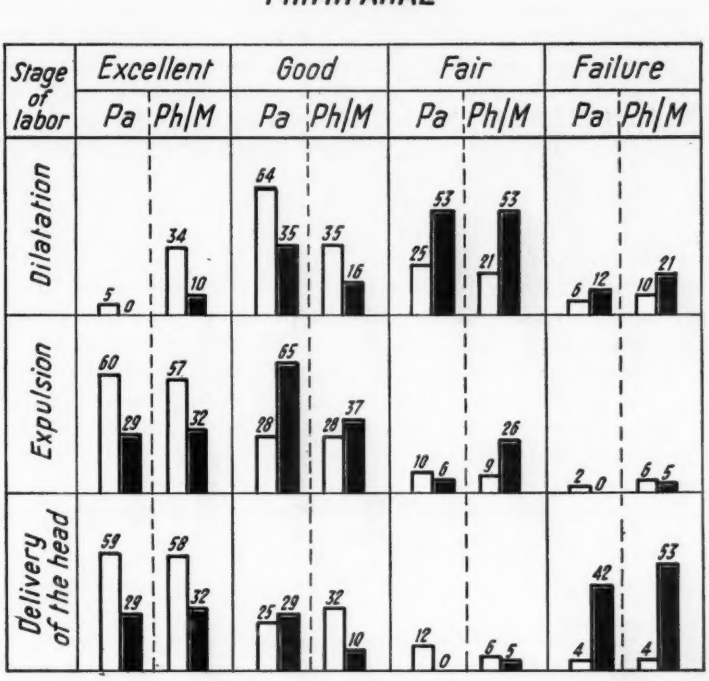


Fig. 4.—Appraisal of the course of delivery in primiparas with and without psychoprophylactic preparation (PPP): 56 cases with and 20 without PPP. Same representation as in Fig. 3.

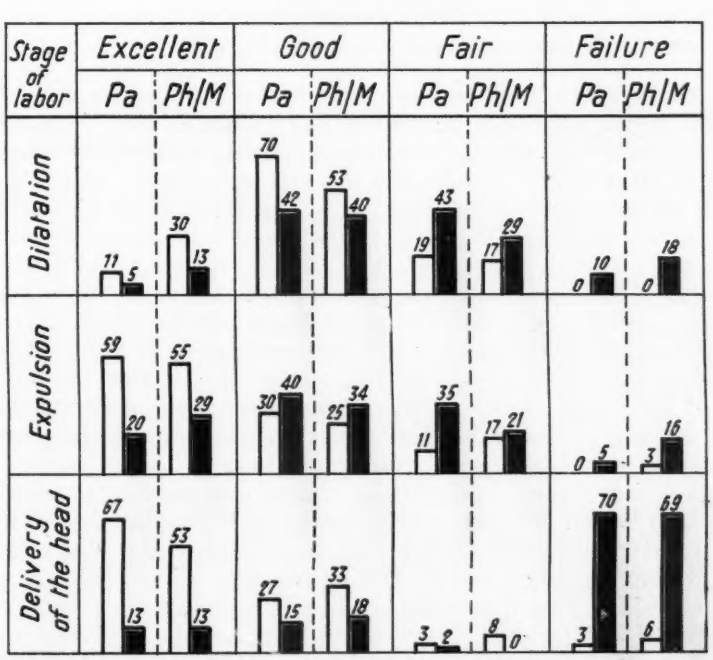


Fig. 5.—Appraisal of the course of delivery in multiparas with and without psychoprophylactic preparation (PPP): 36 cases with and 39 without PPP. Same representation as in Fig. 3.

The incidence of obstetrical operations has not been influenced in our department by the introduction of psychoprophylactic preparation (Table X). The higher percentage of cesarean sections in the nonprepared group is easily explained: Pregnant women for whom a prophylactic operation has been planned beforehand did of course not undergo a psychoprophylactic training; neither did expectant mothers with complications of late pregnancy like placenta previa or toxemia, which later on became the cause of the abdominal delivery. The incidence of forceps extractions was low in both groups and the slight decrease in the series of conditioned parturients may not be significant, since our material is still small. We were rather liberal with episiotomies, notwithstanding the psychoprophylactic preparation. In our opinion this procedure is advantageous for future perineal support, even in patients with perfectly relaxed perineal muscles. The higher figure for episiotomies in the group of conditioned women is probably due to the higher percentage of primiparas among them. In several of our conditioned patients we were obliged to induce labor, but this procedure did not interfere with the success of the psychoprophylactic method.

TABLE X. INCIDENCE OF OBSTETRICAL OPERATIONS IN PREPARED AND NONPREPARED PARTURIENTS
(Jan. 1, 1955, to June 30, 1956)

OPERATION	PPP* (%)	NONPREPARED (%)
Cesarean section	2.8	4.4
Forceps midpelvis	1.9	2.6
Forceps outlet	0.9	1.4
Medication or operation for cervical dystocia	1.2	0.5
Episiotomy	53.0	34.0
Breech, classical	0.3	0.4
Extraction by Bracht maneuver	2.6	3.7

*PPP = psychoprophylactic preparation.

The introduction of the psychoprophylactic preparation has modified the use of other procedures for obstetrical analgesia in our department. The number of patients who had no medical analgesia whatsoever increased from 2.5 per cent in 1954 to 35.5 per cent in the first semester of 1956. The incidence of analgesia with Trilene or nitrous oxide has sharply decreased and the use of chloroform during the delivery of the head has almost been abandoned (Fig. 6).

Injections of Demerol have been given much less frequently during the last eighteen months. Only a little more than one fourth of all our parturients have undergone a psychoprophylactic training. The decrease in the use of other analgesic procedures is so important that it can be explained only by a higher incidence of deliveries without analgesia also in the group of unprepared women. Since the day when we introduced the psychoprophylactic method in our Department, the atmosphere in the delivery room has in general become more calm. Oxygen is almost systematically administered to conditioned and unconditioned parturients, both are taught to breathe correctly, and receive adequate advice and encouragement. We believe that all these changes have made possible the spectacular diminution of medical obstetrical analgesia. The incidence of lumbar peridural analgesia, however, has not changed. This procedure several years ago replaced saddle block which was frequently followed by bad and prolonged headaches and in our experience continuous peridural analgesia is easier to administer than continuous caudal analgesia. Peridural anesthesia has rarely been used for mere

analgesia, but has in general been administered with the purpose of releasing a cervical spasm and the contraction of lumbar and pelvic muscles. We consider it, furthermore, as a very suitable anesthesia for most cesarean sections.

Mothers who had been delivered of their first child under medical analgesia of any type and later on had psychoprophylactic preparation for their second childbirth almost invariably preferred this latter method, which gave them a feeling of a personal achievement and of deep satisfaction.

About 50 per cent of all patients who had undergone psychoprophylactic preparation declared spontaneously immediately after the delivery that they would be ready to use the same method for another childbirth.

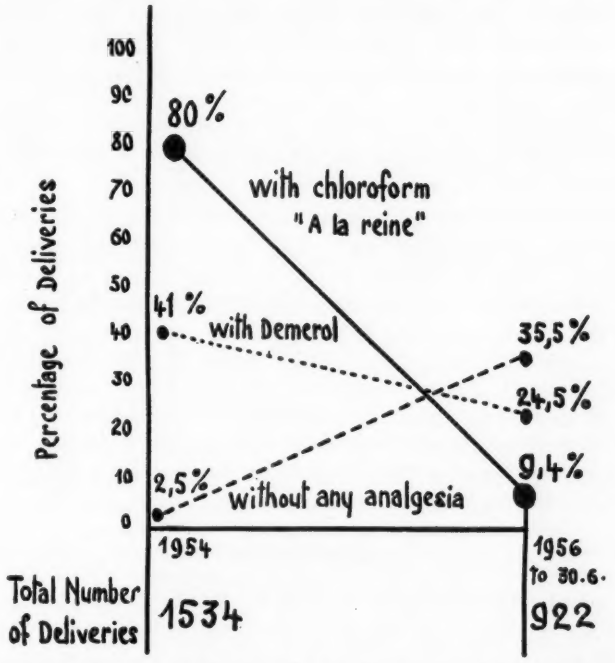


Fig. 6.—Incidence of obstetrical analgesia with chloroform and Demerol before and after the introduction of psychoprophylactic preparation.

As already mentioned 25 per cent of our conditioned parturients complained of pains and accepted some medical analgesia in spite of the psychoprophylactic training. There is no reason why we should refuse these patients medical alleviation of their pains. In most of these cases, however, the psychoprophylactic preparation has not been completely useless as it postponed the moment when medication became indicated and reduced the necessary amount of analgesics.

The failures we observed had various reasons; incorrect application of the method may have been responsible for many of them, especially in the first months after its introduction. Among the numerous mistakes which may occur we may mention incomplete or inadequate teaching, bad timing of the lectures, unsuitable delivery rooms, insufficient or not specially trained personnel, interference of family members not acquainted with the method. In other patients the failures may be due to obstetrical causes as, for instance, an abrupt onset of violent and frequent contractions which leave no time for the patient to control herself. A prolonged labor, on the other hand, will exhaust the patient's energy and break down her nervous resistance so that she

can no longer set in motion the conditioned reflexes. In a third and important group, the failure is due to the psychic condition of the parturient.

In multiparas it is the memory of prior painful deliveries which often impairs the conditioning. Another cause is fear of an abnormal or stillborn baby, especially in sterility cases or in patients who had already had such an experience. Moral problems may interfere, the child may be consciously or subconsciously rejected by the expectant mother. On the other hand there are women who regret the separation of the fetus whom they felt moving in their body and they are afraid of the childbirth which appears to them like the painful loss of a limb. A prerequisite for the success of psychoprophylactic preparation is a sufficient degree of intellectual development.

Highly intelligent but hypersensitive patients, on the contrary, frequently had excellent deliveries, but complained bitterly afterward of the pains provoked by subcutaneous injections or stitches for perineal repair for which they had not been conditioned. At present my colleague Roux is performing different psychotechnical tests on the expectant mothers who follow the preparatory course in order to study which are the most favorable psychological types and in which cases the method is likely to fail.

It has been said that women who failed to have an easy childbirth after psychoprophylactic preparation may feel frustrated and may develop an inferiority complex. This is easy to avoid by explaining to the patient that she is not responsible for the failure and that analgesics have been required by a particular obstetrical condition. It would certainly be a pitfall of the method if one should forget other obstetrical analgesics which still remain valuable in certain situations. Another shortcoming would be an excessive endeavor to maintain "natural" childbirth at any price. This attitude may lead to the infraction of classical laws in obstetrical practice, such as omission of periodical examinations of the expectant mother and delay in the performance of obstetrical interventions.

Conclusions

We should not consider psychoprophylactic preparation, natural childbirth, or whatever we may call it as a revolutionary method which is contrary to the classical practice of obstetrics, but we should use it as a valuable addition to our basic therapeutic means. Without having a direct influence on the pathology of childbirth this psychological preparation will render the delivery easier in normal cases and will make the patient more cooperative when a special difficulty arises and sedation, medication, or operation becomes necessary. Considering to what a great extent tension may be relieved and pain diminished by simple physical exercises associated with adequate psychological preparation, one wonders if these principles should not be applied much more generally to the practice of medicine. Our first task is, of course, to fight with all weapons the disease itself. On the other hand, we should never forget that we are not merely dealing with a medical problem, but also with a suffering human being, whose reaction to the disease should not be neglected. If a patient is given a simple explanation of the nature of his ailment and the rationale of the applied therapeutic procedure, he may accept more easily his situation, he may feel less pain and may cooperate more actively with the physician. It may be that a patient's good psychological adjustment facilitates and accelerates his cure, but there is no doubt that this

adjustment will ease his moral and physical suffering. This leads me to point out again that the physician should not become exclusively a biological scientist, but should take care not only of the physical state but also of the moral condition of his patient.

With regard to the psychoprophylactic preparation for easing childbirth, I can only say that its practice has been a gratifying experience to me by which I learned again how great a power the spirit can exert over the body.

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STUDIES ON LACTIC ACID METABOLISM IN PREGNANCY AND LABOR*†

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THE formation of excessive lactic acid in response to acute metabolic demands in the face of (presumably) temporarily inadequate tissue oxygen is a commonly recognized phenomenon. For example, in any form of vigorous exercise, the muscular demands for oxygen cannot long be met on a pay-as-you-go basis, but must be supplemented by the function of anaerobic metabolism, wherein energy stored in glycogen is liberated with the ultimate formation of lactic acid. Such a source of energy is particularly inefficient in terms of calories produced, since "for each gram mol. of lactic acid produced the free energy amounts to about 29,000 calories, whereas some 325,000 calories are liberated by the oxidation of a corresponding amount of lactic acid to carbon dioxide and water."[1] On the other hand, when considered as a "time utility," even this inefficient form of energy release is of tremendous value, since by this means the organism is enabled to function without harm for brief periods in the absence of oxygen.

Some knowledge of anaerobic metabolic processes as they apply to obstetrics should be of consuming interest, since we are dealing with an area where the fetus appears to be deprived physiologically of his normally minimal oxygen supply at frequent intervals during labor; and where a multitude of pathologic processes lie in wait to throw further burdens upon the fetal anaerobic potentialities.

The ability to produce lactate begins very early in fetal life. Villee[2] found evidence of lactate production in fetal tissues of 7 weeks' gestation, and noted no change in its production by most tissues from any subsequent stage of gestation.

This ability to break down glycogen to the lactic acid stage in the absence of oxygen appears to represent at least one protective device which enables the immature fetus to withstand oxygen lack. Himwich and his co-workers,[3-6] for example, demonstrated that the unexpectedly prolonged survival of newborn rats which were placed in nitrogen was accompanied by a tremendous increase in blood lactate. When the animals were injected with enzyme inhibitors (sodium iodoacetate or sodium fluoride), the survival time was shortened to that which would be expected if an adult animal of the same species were deprived of oxygen, and the lactate level was only about one third as high as that of the

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uninjected animals. In addition, hypoglycemia brought about by the injection of insulin hastened the death of the anoxic newborn rat, while the intraperitoneal injection of glucose prolonged the life of the anoxic 8-day-old rat.

There is evidence that the Himwich observations in newborn rats hold true in some degree for human newborn infants. Räihä[7] described an excessive excretion of pyruvic and lactic acids in the human newborn. Wilson and associates[8] believed that the "periodic respiration" of premature newborn infants is an expression of the persistence of anaerobic metabolic habits of the infants, and these workers point out that anaerobic utilization of glucose may have a bearing on the food requirements of such infants.

In adult life, too, a chronic partial deprivation of oxygen by cardiopulmonary disease may throw the mature individual to an increased extent back upon anaerobic metabolic resources. Huckabee,[9] in studying cardiac patients, found that they "relied on chemically anaerobic mechanisms to meet cellular energy requirements much more than normal subjects," and that "patients with diseased hearts increased cardiac output by only 30 to 60 per cent as much as called for by metabolic needs, and only 50 to 80 per cent of oxygen required by the tissues was delivered, despite increased blood oxygen extraction; the remainder of total energy expenditure was supplied by peripheral tissue anaerobic mechanisms (61 to 185 mg. O^2 equivalents per minute)." Wright[10] has found that lactic acid levels in patients with cardiopulmonary disease tend to be disproportionately elevated by physical activity, and to return to normal levels very slowly: in severe cardiac failure, the lactic acid level remains permanently elevated. Kleeberg and Gitelson[11] found high pyruvic acid values in patients with congestive heart failure, the elevations being somewhat in proportion to the severity of the disease.

Several observers have reported on fetal-maternal relationships of lactic acid. Their divergent findings have given rise to some confusion. In 1928, Blair Bell[12] found umbilical cord blood lactic acid to be about twice that of maternal venous blood. He also found that the umbilical arterial blood level exceeded that of the umbilical venous level, and concluded that the fetus at term must produce significant amounts of lactic acid. Eastman and McLane[13] in 1931 reported normal blood lactic acid levels in the fetus, but elevated figures at birth. They believed that in normal infants the increased blood lactic acid content at birth was due to simple diffusion from the mother, rather than the result of endogenous fetal production. They found, however, an endogenous rise in fetal blood lactic acid in cases of fetal asphyxia. In the following year Loeser,[14] in a more extended study involving both human and animal work, made the following observations. In humans, he found that the maternal blood lactic acid levels were consistently elevated, averaging 30.5 mg. per cent. During labor, he found that umbilical vein blood levels exceeded maternal arm vein levels and also umbilical arterial levels; this he interpreted as an indication that the placenta rather than the fetus produced the excessive amount of lactic acid. Working with animals, he found, in the limited number of experiments he was able to complete, that in pregnant rabbits the concentration of lactic acid in the uterine vein exceeds that in the uterine artery. In cat fetuses, he also noted that vena caval levels were lower than were those of the uterine vein.

The present report concerns studies carried out with the hope of clarifying some of the observations made by previous workers, extending the study of lactic acid metabolism in the human to a larger series of infants and mothers, and, if possible, of bringing the conclusions into the sphere of clinical usefulness.

Material and Methods

Blood lactic acid determinations were carried out on various groups of subjects, including pregnant patients, patients in labor and in the puerperium, and nonpregnant controls. In addition, fetal and placental blood and amniotic fluid determinations were run. The adult subjects had been resting at least 30 minutes, and the majority were fasting; the remainder had had a light breakfast at least 2 hours previously. All specimens were secured without use of a tourniquet, collected in bottles containing sodium fluoride to act both as an anticoagulant and also as a deterrent to glycolysis, and immediately refrigerated. Determinations (method of Barker and Summerson: J. Biol. Chem. 138: 535, 1941) were begun within 4 hours in every instance.

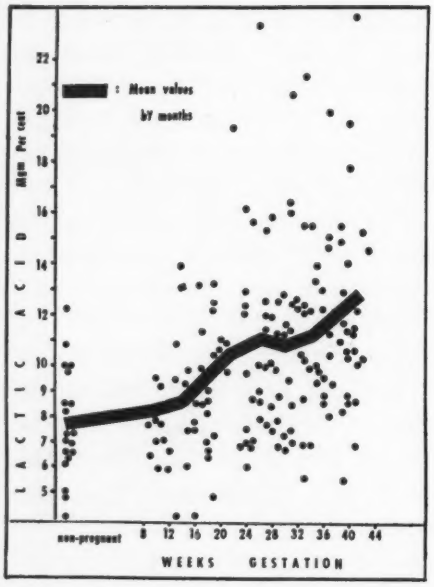

Fig. 1.—The mean resting blood lactic acid level rises from 7.69 mg. per cent in the nonpregnant subject to 12.84 mg. per cent in the patient in the 41 to 43 weeks' pregnancy range.

Results

A. Alterations in Blood Lactic Acid During Pregnancy.—

Blood lactic acid determinations were carried out on 188 patients, of whom 19 were nonpregnant controls, 140 were pregnant but not in labor, and 32 were from ½ hour to 3 days post partum. A total of 205 determinations were done on this group, 19 of the patients having two or more tests. The results, shown in Table I and Fig. 1, are arranged according to menstrual weeks of pregnancy. There is noted a fairly consistent climb in the mean values, starting from a level of 7.69 mg. per cent in the nonpregnant subjects, and rising to 12.4 mg. per cent in the patients who were from 41 to 43 weeks pregnant. Beyond 40 weeks' gestation, the maternal lactic acid blood level averaged approximately 66 per cent

above that of the controls. The range of individual values was a wide one, varying from 4.0 to 25.3 mg. per cent in the pregnant patients. All values above 13.2 mg. per cent in our laboratory were found in patients who were at least 22 weeks pregnant.

TABLE I. LACTIC ACID VALUES IN NORMAL PREGNANCY

WEEKS OF GESTATION	NO. IN GROUP	RANGE (MG. %)	MEAN LACTIC ACID VALUES (MG. %)	MEDIAN (MG. %)
Nonpregnant	19	3.8 -12.2	7.69	7.5
9-12 weeks	11	5.9 - 9.5	8.27	7.1
13-16 weeks	13	4.0 -13.0	8.56	8.8
17-20 weeks	18	4.8 -13.2	9.45	9.5
21-24 weeks	13	6.0 -19.3	10.56	9.8
25-28 weeks	20	6.8 -23.3	11.17	10.2
29-32 weeks	19	6.65-20.6	10.81	9.9
33-36 weeks	25	5.6 -21.3	11.18	10.5
37-40 weeks	25	5.5 -19.9	12.07	11.42
41-43 weeks	9	6.8 -25.3	12.84	12.4
Post partum:				
½-1 hour	14	9.4 -23.4	14.24	13.4
12-48 hours	9	7.2 -11.8	9.69	9.9
49-72 hours	10	5.95-16.1	9.11	8.7
Total	205			

Regardless of the immediate significance of the elevated lactic acid, it might be assumed that the mechanism involved in producing the elevation would include one or more of the following:

1. Increased maternal formation.

2. Increased formation of lactic acid by the uterus and/or its contents. If this should be the case, the absolute maternal blood acid values in late pregnancy would be even higher than indicated above, due to the increased blood volume.

3. Delay of reconversion of lactic acid back into glycogen by the maternal structures. Loeser[14] found that in the pregnant rabbit about twice as much time was required for blood lactate levels to return to normal following the injection of lactate as compared to the time required by the nonpregnant control.

That the source of at least part of such lactic acid elevation is the uterine contents is indicated by the indirect experiment described below.

B. Lactic Acid "Uterine Flush-out" Studies.—

There is good evidence that during uterine contractions a large component of the uterine venous blood is squeezed back rapidly into the central venous reservoir, and thence distributed to the maternal systemic circulation until the uterus relaxes, when uterine filling can again take place.[15] If any given metabolite appears within the uterine circulation in amounts greater than the amount present in the general circulation, it should be possible to demonstrate this fact by indirect study. For example, Palmer and Walker[16] showed that during a uterine contraction the arteriovenous oxygen difference in the blood presented to the heart was significantly higher than during uterine relaxation, indicating that the oxygen extraction ratio was higher in the uterine than in the systemic circulation. The present study was carried out as follows. With the subject in labor, an externally recording tokodynamometer* was attached to the anterior abdominal wall for timing of uterine contractions. An Cournand-type

*Manufactured by Statham Laboratories, Inc., and generously donated by Wyeth Laboratories, Inc., Philadelphia, Pa.

TABLE II. FETAL AND MATERNAL LACTIC ACID LEVELS AT CESAREAN SECTION DELIVERIES

NAME	IN LABOR?	WEEKS OF GESTATION	ANESTHETIC	FETAL DISTRESS	AMNIOTIC FLUID (MG. %)	UMBILICAL ARTERY (MG. %)	UMBILICAL VEIN (MG. %)	UTERINE VEIN (MG. %)	MATERNAL ANTECUBITAL VEIN (MG. %)
H. B.	No	39	Spinal		56.2	22.1	18.55	11.65	10.28 (D–4)*
								12.3	9.9 (D+22)
M. D.	No	40	Spinal		67.0	31.2	17.85	14.1	11.42 (D–16)
L. B.	Yes	42	Spinal			---	31.0	23.7 (D–3)	18.2 (D–15)
E. C.	No	42?	Spinal	? mod. placental insufficiency	69.6	16.85	16.2	11.55	12.45 (D–6)
								21.82	17.12 (D+8)
R. B.	No	39	Spinal		82.4	15.4	17.0	15.95	11.75
M. M.	No	39	Spinal		62.2	---	13.9	---	15.5
R. M.	No	39	Spinal		74.0	20.1	12.4	10.9	5.54
H. H.	No	41	Spinal		63.50	22.10	13.85	13.10	8.63
B. S.	No	43	Cyclopropane (failed) (spinal)		52.70	16.10	14.23	11.24	10.70 (D–2)
								16.86	13.29 (D+6)
M. Mc.	No	40	Spinal		77.50	---	---	13.32	11.15
								18.00	17.86
H. E.	No	38	Spinal		80.8	17.6	16.4	---	---
N. E.	No	40	Spinal		93.4	35.4	23.1	17.2	13.0
H. A.	No	41	Spinal		66.5	38.6	11.1	11.2	10.7
D. U.	No	40	Spinal		---	18.9	18.3	---	---

*D-4 = 4 minutes before delivery.

needle inserted into the maternal brachial artery was connected by an attached tube to a Rothe sample collector,[17] which allows precision in timing during the sampling. Arterial specimens were taken continuously, each tube representing a 2 second flow. Analysis for lactic acid was done in most instances on the pooled specimen from a 4 second flow, and in the remainder on the blood from a 6 second flow.

Fig. 2 shows a typical result. In this study, carried out for 3 minutes, the curve of arterial lactic acid values mirrored alterations in uterine tone quite faithfully. With each increase in uterine tone, there was seen a consistent subsequent rise in maternal arterial lactic acid. The maternal blood level approximated 13 mg. per cent during the uterine resting phase, and 15 mg. per cent during the active phase of the contraction cycle, thus exhibiting about a 15 per cent higher systemic level following the onset of a uterine contraction. Comparable alterations in maternal arterial lactic acid levels were found in each of the seven "flush-out" experiments run. The consistent lag in timing between the peak of uterine contraction vs. the peak level of arterial lactic acid is believed to represent the time required for the lactic-acid-contaminated uterine blood to traverse the augmented central venous pool and thence to appear in the arterial circulation.

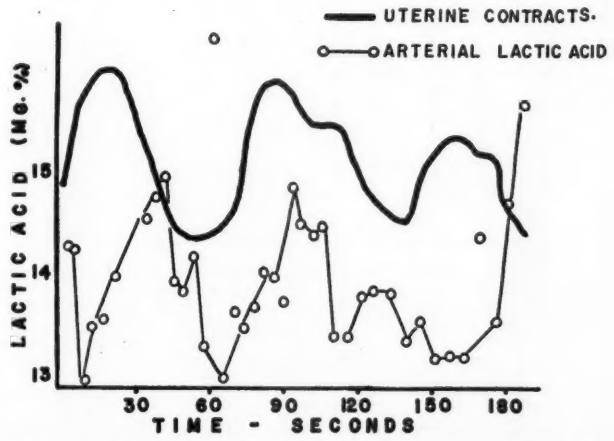

Fig. 2.—Lactic acid "uterine flush-out" study. Uterine contractions were associated with the subsequent appearance of increased lactic acid levels in the brachial artery.

This experiment indicates that, at least in conditions of active labor, substantial amounts of lactic acid appear in the uterine circulation, and that the excess uterine lactic acid is eventually distributed to the systemic circulation.

There is no way of interpreting from this experiment, however, the relative amounts of this excess lactic acid contributed by any of the primary metabolic units concerned, i.e., the fetus, the placenta, and the uterus itself.

In the following experiments, an attempt was made to define the role of the fetus in the production of lactic acid under normal intrauterine conditions.

C. Simultaneous Fetal-Maternal Studies.—

1. At cesarean section, 14 patients were studied. In the majority of cases, the indication for section was previous section. Only one of the subjects was definitely in labor. The gestations ranged from 38 to 43 weeks. All patients appeared relaxed, were not making voluntary physical effort, and had been fasting at least six hours. All but one subject received spinal anesthesia: the remaining patient was given cyclopropane. Specimens were secured from the following sources and in this approximate sequence: (a) maternal arm vein, at

TABLE III. FETAL AND MATERNAL LACTIC ACID LEVELS AT VAGINAL DELIVERY

SUBJECT	WEEKS OF GESTATION	ANESTHETIC	FETAL DISTRESS	AMNIOTIC FLUID (MG. %)	UMBILICAL ARTERY (MG. %)	UMBILICAL VEIN (MG. %)	MATERNAL ANTECUBITAL VEIN (MG. %)
P. S.	40	Spinal	Membranes yellow stained	-	60.80	51.70	24.80 (D)*
E. T.	36	Caudal	Moderate asphyxia	94.3	---	49.755	11.83 (D)
G. P.	41	Caudal		78.8	35.0	23.0	25.25 (D–19)
J. M.	41	Caudal + N_2O + O_2		85.0	38.5	21.7	8.35 (D-8 quiet) 33.9
A. W.	41	Ether	Amniotic fluid green-yellow				9.75 (D–67) 15.8 (D–1) 21.5 (D+16)
S. P.	40	Caudal	Fetal heart irregular in utero. Depressed at birth	85.0	22.3	17.3	12.3 (D–12) 13.3 (D+3)
D. S.	42		Moderate meconium stain	---	25.6	16.7	7.60 (D–14) 14.3 (D+9)
J. E.	34			---	14.5	12.05	10.15
F. D.	40						19.3 (D–19)
(twins)				68.8	28.9	26.05	20.3 (D)
				67.6	---	21.61	21.9 (D)
J. C.	42	Spinal	Fluid bright yellow	71.7	16.6	14.05	15.12 (D–3) 13.4 (D+13)
H. R.	31	Spinal	Mild respiratory depression	---	52.3	40.5	22.2 (D–2) 20.9 (D+1)
R. W.	43			63.4	---	18.9	9.9 (D–12) 33.8 (D)
B. H.	38	Gas-oxygen-ether		73.4	28.2	17.4	12.05 (D–30) 17.8 (D+1)
I. B.	40	Spinal		---	30.2	24.1	18.1 (D+2)
J. D.	41			114.1	---	---	13.5 (D–1)
D. H.	40		Moderate meconium stains. Some "fetal distress"	82.3	100.3	81.3	20.7 (D–3) 16.25 (D+8)
O. R.	40			108.8	40.3 (D+3)	12.25 12.15	11.16
F. H.	41	Caudal	Infant stained deep yellow. Delay in breathing 1 minute	---	38.95	23.90	17.60 (D) 15.20 (D+15)
C. L.	38	Spinal		69.9	17.6	13.9	---
L. E.	39	Spinal		94.0	22.2	21.3	---
B. A.	39	Spinal		79.2	25.3	---	---
D. O.	39	Spinal		92.8	18.0	17.3	---
C. U.	41	Spinal		---	24.9	14.8	17.4
P. O.	39	Spinal		105.4	32.2	21.6	---

*D-4 = 4 minutes before delivery.

the time the abdominal incision was made, (b) amniotic fluid, either directly through the uterine wall, or through the uterine incision, (c) simultaneously, if possible, uterine vein and maternal arm vein, (d) umbilical artery and vein immediately upon delivery of the infant, (e) a postdelivery specimen from uterine vein and maternal arm vein.

The results are indicated in Table II. There may be seen a very definite gradient, descending progressively from amniotic fluid, through umbilical artery, umbilical vein, uterine vein, and maternal antecubital vein. The fact that the blood coming from the fetus held the highest level of lactic acid indicates that at least some (and probably most) of the excess of this metabolite is being produced in the fetus, and then finds its way back across the placenta to the maternal circulation. This relationship is graphed in the results obtained from a single subject (Fig. 3).

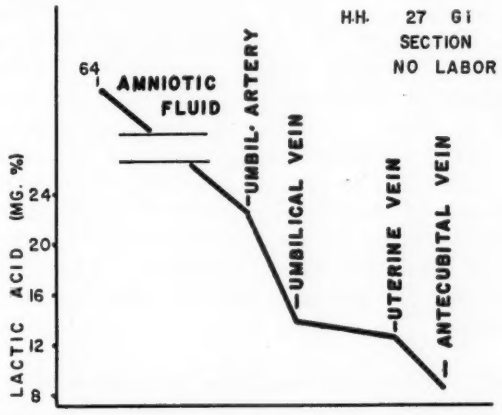

Fig. 3.—Showing the maternal-fetal lactic acid relationships in a representative case. The descending gradient of values through umbilical artery, umbilical vein, uterine vein, and maternal arm vein is an almost constant finding, and appears to indicate production of lactate by the fetus, extraction by the placenta, and subsequent passage of at least a part of the lactate to the maternal circulation.

Perhaps the most significant finding is that in the 11 subjects in whom both umbilical artery and umbilical vein specimens were secured, the average arterial lactic acid level was 23.12 mg. per cent, while the average level in the blood being returned from the placenta to the fetus was 16.27 mg. per cent, a difference of 6.85 mg. per cent. In other words, on the average, 29.63 per cent of the fetal arterial lactic acid is removed in a single circuit through the placenta. It is apparent, then, that a significant amount of lactic acid is being continuously produced by the fetus in late gestation, and continuously removed. While it is impossible to state categorically that this condition indicates response to a chronic oxygen deficiency, such an explanation appears quite logical. As a matter of fact, such a situation in utero would seem somewhat analogous to that of Huckabee's patients with congestive heart failure, who also had a chronically elevated blood lactic acid level.

2. A further 24 patients were studied during vaginal delivery (Table III). The gradient here moves in the same direction as was seen in the cesarean section patients, but there were quantitative differences, probably associated with the fact that these patients had experienced labor. In the 19 of these cases in which both umbilical arterial and umbilical vein values were obtained, the average arterial level was 34.07 mg. per cent, while the average vein level was 24.78 mg. per cent, the mean values in each case being much larger than those obtained in the infants whose mothers had not experienced labor. The average

elimination of lactic acid by a single passage through the placenta was 9.29 mg. per cent. While this is over one third greater than the amount cleared when compared to that of infants not subjected to labor, the percentage clearance by a single passage varied but slightly, being 27.27 per cent.

It is possible to express the degree of removal of lactic acid from the fetal organism in terms of that fraction of extraction completed in a single circulation through the placenta, thus:

$$\text{COEFFICIENT OF PLACENTAL EXTRACTION} = \frac{\text{Lactic acid umbilical artery} - \text{umbilical vein}}{\text{Lactic acid umbilical artery}}$$

Tables IV and V indicate the placental extraction ratios for the cesarean section group and for the vaginal delivery group, respectively. The rather wide range of values in both groups is quite apparent, but the spread is no greater than that obtained by others in working on related fetal-placental problems—for example, the fetal "coefficient of oxygen utilization" derived through the same sort of calculations by Romney and co-workers.[18] If the averages of the two groups are considered, the coefficient of lactic acid extraction changes relatively little as a result of labor. Considered quantitatively, however, it is interesting to note how much additional lactic acid can be eliminated from the fetal organism during labor in the face of a relatively constant extraction coefficient. It appears that any need for increased elimination of this metabolite can be easily accomplished simply by the accumulation of a sufficient concentration of lactic acid on the fetal side of the placenta. The coefficient of extraction, it may be pointed out, assumes a relatively constant rate of flow of fetal blood through the placenta.

TABLE IV. COEFFICIENT OF LACTIC ACID EXTRACTION
TERM PREGNANCY: NO LABOR

SUBJECT	UMBILICAL ARTERY (MG. %)	UMBILICAL VEIN (MG. %)	ARTERIOVENOUS DIFFERENCE (MG. %)		LACTIC ACID DIFFERENCE UMB. ART. – UMB. VEIN LACTIC ACID CONTENT UMBIL. ARTERY
H. B.	22.1	18.55	3.55		0.1606
M. D.	31.2	17.85	13.35		0.4279
E. C.	16.85	16.2	0.65		0.0386
R. B.	15.4	17.0	–1.60		–0.1039
R. M.	20.1	12.4	7.70		0.3831
H. H.	22.1	13.85	8.25		0.3733
B. S.	16.1	14.23	1.87		0.1161
H. E.	17.6	16.4	1.2		0.0682
N. E.	35.4	23.1	12.3		0.3474
H. A.	38.6	11.1	27.5		0.7124
D. U.	18.9	18.3	0.6		0.0318
Average for 11 infants not subjected to labor	23.12	16.27	6.85	Coefficient of means	0.2963

The quantitative rise in lactic acid excretion by the fetus during labor remains to be explained. Two physical factors present themselves as possibilities:

1. With the rise in maternal blood lactic acid levels during the course of labor, it may be necessary to raise the lactic acid level in the placenta to maintain an effective gradient between the placenta and the maternal circulation. But an examination of Table III shows that the average rise in maternal systemic lactic acid levels is not large, in a numerical sense, and thus not likely to be responsible for the much larger relative increase in fetal lactic acid concentration.

2. The second factor offers a more likely explanation for the increased fetal excretion during labor. This is the fact that with a vigorous uterine contraction, the arterial supply to the uterus may be temporarily shut off,[19] and thus the fetus may in effect have to depend upon its anaerobic resources during a portion of each uterine contraction cycle. If the amount of blood actually delivered to the fetus with the uterus at rest is no more than minimumly adequate, one might anticipate a progressive rise in fetal lactic acid production as one effective contraction followed another in late labor. It is even possible that some fetuses live in such precarious oxygen balance that they could not survive the process of labor if they were unable to mobilize additional energy from anaerobic sources.

TABLE V. COEFFICIENT OF LACTIC ACID EXTRACTION AFTER VAGINAL DELIVERY

SUBJECT	UMBILICAL ARTERY (MG. %)	UMBILICAL VEIN (MG. %)	ARTERIOVENOUS DIFFERENCE (MG. %)	LACTIC ACID DIFFERENCE UMB. ART. – UMB. VEIN LACTIC ACID CONTENT UMBIL. ARTERY
P. S.	60.80	51.70	9.10	0.1497
C. P.	35.0	23.0	12.00	0.3429
J. M.	38.5	21.7	16.80	0.4364
S. P.	22.3	17.3	5.0	0.2242
D. S.	25.6	16.7	8.9	0.3477
J. E.	14.5	12.05	2.45	0.1690
F. D. (twins)	28.9	26.05	2.85	0.0986
J. C.	16.6	14.05	2.55	0.1536
H. R.	52.3	40.5	11.8	0.2256
B. H.	28.2	17.4	10.8	0.3830
I. B.	30.2	24.1	6.1	0.2020
D. H.	100.3	81.3	19.0	0.1894
O. R.	40.3	12.25	28.05	0.6960
F. H.	38.95	23.90	15.05	0.3864
C. L.	17.6	13.9	3.7	0.2103
L. E.	22.2	21.3	0.9	0.0405
D. O.	18.0	17.3	0.7	0.0389
C. U.	24.9	14.8	10.1	0.4056
P. O.	32.2	21.6	10.6	0.3292
Average for 19 infants delivered vaginally	34.07	24.78	9.29	Cofficient of means 0.2727

D. Changes in Maternal Lactic Acid During Labor and Post Partum.—

During the course of labor, the maternal blood lactic acid level rises. Fig. 4 indicates graphically the changes observed in a single labor. This case was of particular interest because the patient remained calm and physically quiescent throughout the entire first stage of labor; thus it may be assumed that at least a major portion of the progressive rise in lactic acid concentration is on the basis of activity of the uterus and/or its contents. At rest, before the onset of active labor, this patient's level was 8.0 mg. per cent; then, rising steadily throughout the course of active labor, it reached 13.8 mg. per cent when complete dilatation had occurred. Interestingly enough, the level was essentially unchanged ½ hour later, after the patient had been bearing down with contractions for a short time. The peak level, 19.0 mg. per cent, was attained at the time of delivery, after which it dropped to 12.8 mg. per cent during the ensuing hour.

This pattern is fairly typical of most of the 7 patients who had sequential lactic acid determinations performed throughout at least part of the course of labor. The maternal blood levels reach their maximum at the time of delivery. In a series of 19 patients, delivered vaginally, whose blood lactic acid

was determined within ±4 minutes of the moment of delivery, the average concentration of lactic acid was 19.0 mg. per cent (range 10.2-33.9). On the other hand, in a series of 12 patients who were having cesarean section delivery without prior labor, the mean lactic acid concentration was only 11.6 mg. per cent (range 5.5-15.5): this level is compatible with the levels found in resting outpatient subjects at comparable stages of gestation. It is evident, then, that the process of labor definitely increases the maternal lactic acid concentration, the average rise being in the neighborhood of 64 per cent. Such an increase in maternal concentration of lactic acid relates well to observed fetal changes because, while the maternal rise of 64 per cent is taking place, the average fetal lactic acid (as measured in the umbilical artery, Tables II and III) rises from 23.12 to 34.07 mg. per cent, an increase of about 47 per cent over the levels of infants who have not been subjected to labor and vaginal delivery (Fig. 5).

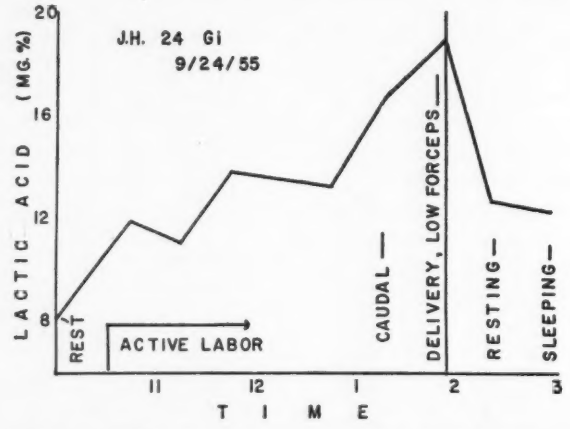

Fig. 4.—The effect of labor upon maternal lactic acid levels. In this patient there was no undue physical exertion, but the lactic acid level more than doubled during the course of labor.

The removal of the fetus, however, does not imply an immediate return of the maternal lactic acid level to nonpregnancy levels. There is always a large drop in maternal levels during the first hour post partum, but the exact amount of the decrease is quite variable. In a series of 14 patients who were ½ to 1 hour post partum, the maternal lactic acid level had dropped to 14.24 mg. per cent, while in 9 patients who were 12 to 48 hours post partum, the average level was 9.69 mg. per cent. By the third day, the level was 9.11 mg. per cent. Thus the maternal level appears to drop within the first hour to near the range of the patient who is pregnant at term but not in labor, and then to drop more slowly toward the nonpregnancy level.

It seems reasonable to believe that one factor contributing to the sustained but small postpartum elevation of lactic acid above the nonpregnancy level may be some combination of circulatory impairment and involutionary processes going on within the uterus itself. Determinations done on a patient at laparotomy 48 hours post partum illustrate this point:

	UTERINE VEIN LACTIC ACID	BRACHIAL VEIN LACTIC ACID
Before oxytocic	15.0 mg. %	14.0 mg. %
4 minutes after administration of Ergotrate, 0.32 mg. intravenously	17.9 mg. %	15.3 mg. %

Similar results were found in a second case. Although the numerical differences here are small, they are consistent, and may indicate a uterine role in sustaining postpartum lactic acid levels.

E. Amniotic Fluid Levels.—

Determination of lactic acid in amniotic fluid was carried out in 52 instances. This included 1 set of twins. One specimen was obtained from the extruded amniotic sac of an 11 weeks' spontaneous abortion and one from hysterotomy at 10 weeks. The remaining specimens were obtained at amniotomy (either at cesarean section or vaginally) in patients ranging from 32 to 43 weeks' gestation. The range was wide: 52.4 to 160.0 mg. per cent (Table VI). The values, however, were consistently high. No constant relationship could be found between amniotic fluid and umbilical arterial values. No significant change was observed relative to different weeks of gestation: in the 9 specimens obtained from patients in the 32 to 38 weeks' gestation group, the average was 76.5 mg. per cent; in 13 specimens at 39 weeks, the average was 79.2 mg. per cent; in 15 specimens at 40 weeks' gestation, the average was 76.2

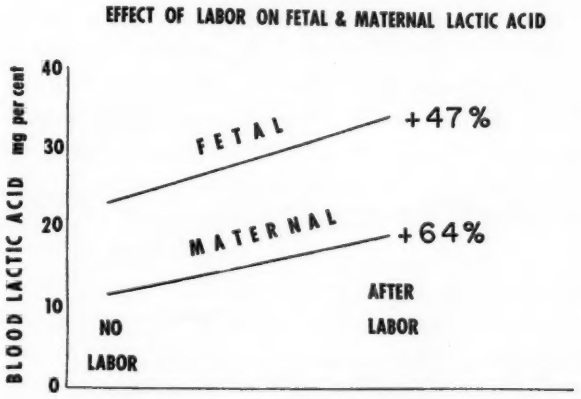

Fig. 5.—Both maternal and fetal lactic acid values rise significantly during labor.

mg. per cent; while in the 13 specimens from the 41 to 43 weeks' group, the average was 78.4 mg. per cent (Fig. 6). There was noted some tendency to a higher amniotic fluid value in patients who had experienced labor before the specimen was taken: in 25 specimens secured from patients who had been in labor, the mean lactic acid value in the amniotic fluid was 82.8 mg. per cent, while in 25 subjects not in labor when the specimen was taken, the lactic acid value was 73.0 mg. per cent. This difference of 13 per cent is probably not of any great significance in view of the rather wide range of concentrations found in both groups.

Several factors may contribute to the maintenance of the high lactic acid levels in amniotic fluid. Since it is known that the human newborn excretes large amounts of organic acids for some time after birth, it is likely that the fetal kidney contributes actively to the high amniotic fluid levels observed in this study. Whether or not glycolysis proceeds within the amniotic cavity has not been documented. And the increasing recognition of the amniotic pool as a very active exchange compartment makes this a worth-while field for further investigation.

F. Clinical Correlations.—

It had been hoped that it might be possible to obtain data which would show in some degree chemically the presence of intrauterine factors denoting potential "placental insufficiency," "fetal embarrassment" in labor, etc. The

value of such a measuring device would be very great, since it might help to indicate certain gestations wherein the fetus would be poorly equipped to withstand labor.

With this in mind, the delivery records of patients on whom blood lactic acid levels were determined have been reviewed. The factors which have been tabulated include such abnormalities as abortion, stillbirth, premature delivery, evidence of fetal embarrassment during labor, unexplained delay in breathing time at birth, and staining of the amniotic fluid. To date, 65 cases have become available for study. Although no definitive conclusions can be drawn from such a small series, it has been interesting to note that the maternal blood lactic acid levels in the majority of cases in which fetal difficulty was destined to occur were *lower* than the average of all the subjects whose specimens were drawn during a comparable antenatal month. Evaluation of the significance of this observation must await the accumulation of a larger series.

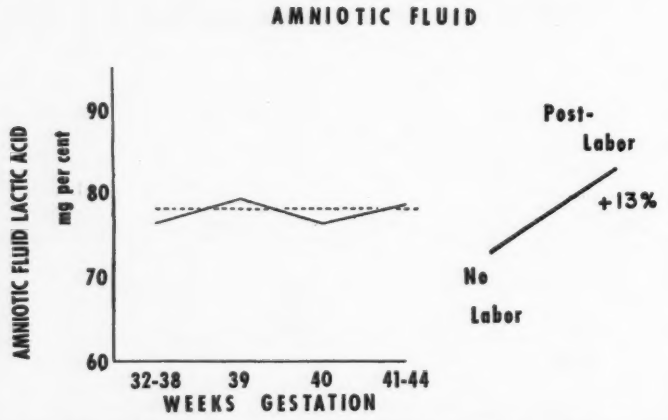

Fig. 6.—The mean amniotic fluid value of lactic acid remains relatively constant during the last trimester, but tends to rise during labor.

Again, the amniotic fluid levels were reviewed in the hope of establishing some quantitative relationship to amniotic fluid staining or fetal distress. Of 6 infants who exhibited amniotic fluid staining, fetal distress, or neonatal respiratory depression, either singly or in combination, the amniotic fluid levels of 4 were very close to the average values obtaining for the entire group of determinations, 77.9 mg. per cent. Two abnormalities were associated with elevated lactic acid levels.

CASE 1.—A patient at 36 weeks' gestation was delivered vaginally of a moderately asphyxiated infant under conduction analgesia. No cause could be ascertained for the respiratory difficulty. The amniotic fluid lactic acid level before the onset of labor was 94.3 mg. per cent, as compared to the mean value of 73.0 mg. per cent in patients who were not in labor at the time the specimen was secured. On the other hand, it may be noted from Table VI that one of the other patients not in labor had an amniotic fluid level even higher, 105.4 mg. per cent, without evidence of fetal embarrassment.

CASE 2.—This patient, in active labor, had yellowish-green amniotic fluid, a specimen of which was secured while she was in active labor. Although no anesthesia was used for delivery, the infant was severely asphyxiated. The amniotic fluid lactic acid level, 160.0 mg. per cent, was the highest for the entire series. Again, though, it may be noted that two other specimens secured while the mothers were in labor were over 100 mg. per cent, but the infants showed no evidence of abnormality.

TABLE VI. AMNIOTIC FLUID LACTIC ACID VALUES

GROUP	NUMBER	LACTIC ACID IN MG. %		
		MEAN	MEDIAN	RANGE
10 weeks' gestation	1	(108.0)		
11 weeks' gestation	1	(104.5)		
32-38 weeks' gestation	9	76.5	73.4	63.9- 94.3
39 weeks' gestation	13	79.2	87.0	56.4-105.4
40 weeks' gestation	15	76.2	77.5	52.4-108.8
41-43 weeks' gestation	13	78.4	69.6	52.7-160.0
No labor prior to amniotomy	25	73.0	69.6	52.4-105.4
Labor prior to amniotomy	25	82.8	79.2	56.4-160.0
All groups above Except 10 and 11 weeks' gestations)	50	77.9	78.1	52.4-160.0

Comment

From the evidence presented, it is believed that the fetus in utero produces a large amount of lactate; and that this production may possibly reflect partially anaerobic metabolism brought about of necessity by a relative deficiency in the oxygen supply available to the fetal tissues. The process is accentuated in labor due to the intermittent diminution of the uterine circulation, the diminution resulting from increased intrauterine pressure at the time of uterine contractions.

If it is true that the fetus must depend in part upon glycolysis for part of its oxidative energy, the presence of a continuous "oxygen debt" is the "normal" state for intrauterine life. The fetus is unique, however, in that it does not "repay" its oxygen debt, but instead the waste product of glycolysis, lactic acid, in this instance, is passed across the placental barrier to the mother for "debt repayment," i.e., reconversion back to glycogen.

It should be pointed out that the measurement of lactic acid fails to tell the entire story of anaerobic metabolism taking place within the pregnant uterus. Pyruvate, for example, rather than being broken down entirely to lactate, appears to follow an independent metabolic pathway, according to the human tissue studies of Villee.[2] However, Kimmelstiel and Villee[20] gave carbon^{14}-labeled pyruvate intraperitoneally to newborn rats, and found that anaerobiosis resulted in a fivefold increase in lactic acid. Thus they felt that "the accelerated glycolysis that was observed is undoubtedly a major factor in survival, but the data do not exclude the possibility that other biochemical or physiological processes of the fetal organism contribute significantly to the ability to withstand oxygen deprivation."

Summary

1. Maternal blood lactic acid levels rise quite steadily during the course of pregnancy, from a mean of 7.69 mg. per cent in the nonpregnant woman to a mean of 12.4 mg. per cent in the patient within the 41 to 43 weeks' gestation range.

2. Uterine contractions during labor cause a transient rise of approximately 15 per cent in the maternal peripheral arterial lactic acid level. This

is interpreted as evidence for increased production of lactate within the uterus and/or its contents.

3. A descending gradient of lactic acid is maintained in fetomaternal relationships, the gradient descending progressively from the highest concentration, found in amniotic fluid, down through umbilical artery, umbilical vein, uterine vein, and maternal arm vein.

4. On the average, 29.63 per cent of fetal arterial lactic acid appears to be removed by a single passage through the placenta when the mother is not in labor. During labor, while the amount of lactic acid removed is much greater, the percentage of extraction remains relatively constant.

5. The mean maternal blood lactic acid level rises by 64 per cent during the course of labor; while the mean fetal rise during labor is 47 per cent.

6. Amniotic fluid levels of lactic acid are consistently high, averaging 77.9 mg. per cent. The process of labor may cause a small additional rise in amniotic fluid lactic acid levels.

I would like to express my appreciation to Mrs. Milena Salehar for the technical help given me in the early part of this project, and to Morris Mandel for his technical aid during the major portion of the project. I would like particularly to express my deep and continuing gratitude to Dr. Allan C. Barnes, whose long-range encouragement and counsel have played such a large part in making this study possible.

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PITOCIN—1955*

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THERE has been a tremendous increase in the use of intravenous dilute Pitocin since 1949. This has been particularly marked in the past five years. The employment of infusions of this oxytocic for the induction and acceleration of labor and for the treatment of uterine dysfunction has been largely an American practice, attracting not too much following in Great Britain, on the Continent, or in the Far East. There is already an extensive literature on the subject. For the steps in its development the reader is referred to the fine papers of Moore and D'Esopo and of Page. Publications from 1951 through 1955, which cover the period of this report, are given in the References. For the most part they are favorable to the method, giving high success rates, low infant loss, and few serious complications. It is probably unfortunately true that not all the complications, particularly ruptures of the uterus, are reported. Nevertheless, the general impression is that infusions of dilute Pitocin constitute a safe and efficient practice for a variety of conditions affecting the onset and conduct of labor.

This study attempts to define the magnitude of usage and the results as they affect mother and child in a sufficiently large and broad sample to give some reflection of current American practice.

The reliability of data depends not only on its accuracy but also on the size and distribution of the sample. These data were taken from "The Obstetrical Statistical Cooperative," a group of obstetrical services that, beginning in 1951, agreed that it would be of mutual advantage to gather their statistics in a uniform manner and to pool them for publication of reports just such as this. All services concerned employed trained, paid personnel for collection and recording of their data. Definitions were fixed at the outset of the project and never thereafter changed without consent and agreement of all concerned. All data were recorded on punched cards with duplicates filed in a central area. These data now constitute a sufficiently large modern sample to preclude changing obstetrical techniques and customs.

For the vast majority of cases in this study, 1 ml. of Pitocin (Parke Davis, 10 I. U. per milliliter) was diluted in 1,000 to 1,500 ml. of 5 per cent dextrose in water and administered at a rate of 20 to 50 drops per minute. Contraindications were those compatible with safe and conservative obstetrics.

*Presented at the Sixty-seventh Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Va., Sept. 6 to 8, 1956.

Table I records the over-all frequency of the use of Pitocin in the cooperating hospitals. The number of private patients for each service is also given for, as will be seen later, this factor exerts a profound influence on the rate of employment of oxytocin. The hospitals concerned are almost all university affiliated, many being medical school center hospitals. This fact alone furnishes a conservative bias to the study. The geographical distribution of the services is not particularly good, being confined largely to the east coast with an overly prominent New York influence. The size of the sample is adequate; 63,276 deliveries in the five-year period from the ten hospitals with 5,656 instances of the administration of Pitocin. The variation in the number of deliveries per service illustrated in Table I reflects not only a difference in size, but also the length of time a service has been a member of the cooperative. Some, such as Grace-New Haven, have but recently joined while others have resigned or been dropped.

TABLE I. TOTAL USE OF PITOCIN IN 63,276 DELIVERIES BY HOSPITAL

	TOTAL DELIVERIES		PITOCIN	
HOSPITAL	NUMBER	PER CENT PRIVATE	NUMBER	PER CENT
Beth El	3,411	88.7	949	27.8
Johns Hopkins	2,696	25.4	55	2.0
University, Baltimore	13,237	36.1	152	1.1
Sinai, Baltimore	9,611	65.6	1,643	17.1
Kings County	15,834	0.0	491	3.1
Long Island College	6,739	64.4	1,523	22.6
Grace-New Haven	1,053	68.8	75	7.1
Cumberland	1,467	0.0	47	3.2
Colorado General	2,430	3.3	37	1.5
Sinai, N. Y.	6,798	68.7	684	10.1
Total number	63,276	24,600	5,656	
Total per cent		38.9		9.0

The considerable variation in the frequency of use of Pitocin from 1.1 to 27.8 per cent is directly correlated with the percentage of private patients in the hospitals. It also, however, reflects such things as types and amount of analgesia and attitudes of individual obstetricians.

The data are accurate with one limitation. The training program for all the technical personnel has but recently been brought to a desirably high level. There may therefore have been some underreporting of the frequency of use of Pitocin in the early years. In all other respects the data are thought to be accurate.

The indications for administration of an oxytocic prenatally are several. It may be employed to induce labor, to accelerate labor, or to treat cases of uterine dysfunction. Furthermore, in the first two instances it may be employed electively or its use may be indicated by a number of varied complications. The distribution of the data by indication and social status is shown in Table II. Induction includes the use of Pitocin both with and without the rupture of membranes. Failed inductions are not recorded, the method of tabulating the data precluding this information. If, in cases of induction, stimulation was carried on after the onset of labor they are still carried only under the induction heading. In other words, the three major indications listed in the table are mutually exclusive. Of the total of 1,123 inductions, only 153, or 13.6 per cent, were indicated. These were largely on the basis of toxemia, and antepartum hemorrhage, and, in a few instances, diabetes.

Instances of the use of Pitocin in labor other than in dysfunction are grouped under "acceleration." In 3,508 such cases, acceleration was termed

elective, there being no definable dysfunction or other visible complication. The term elective may be a misnomer for it is quite probable that there was a short period of slowing or delay in the labor which, although not strictly definable as dysfunction, indicated the prescribed therapy. It seems highly improbable that this group of well-trained and seasoned obstetricians would use a potentially dangerous drug to satisfy personal convenience. Acceleration is recorded as indicated only 136 times, or in 3.7 per cent of such cases. The indication was almost entirely abruptio placentae.

Uterine dysfunction was treated with Pitocin in 1.4 per cent of the total deliveries, or 889 times. It is surprising that, although the original workers on dilute intravenous Pitocin considered this indication to be of prime importance, current practice has found others transcendent. In this series it comprises only 15.7 per cent of the total instances of use of Pitocin and ranks behind acceleration (64.5 per cent) and induction (19.6 per cent).

Table II shows the striking difference between the private and ward services which was alluded to above. This difference does not appear where there is a definite indication, be it under the heading of induction or acceleration or dysfunction. But where the drug is employed electively, the social difference in these two combined is almost fivefold.

TABLE II. TOTAL USE OF PITOCIN IN 63,276 DELIVERIES BY SERVICE STATUS

	PRIVATE		WARD		TOTAL	
	NO.	%	NO.	%	NO.	%
Induction, elective	845	3.4	125	0.3	970	1.5
Induction, indicated	92	0.4	61	0.2	153	0.3
Acceleration, elective	3,000	12.2	508	1.3	3,508	5.6
Acceleration, indicated	72	0.3	64	0.2	136	0.2
Dysfunction	382	1.6	507	1.3	889	1.4
Total	4,391	17.9	1,265	3.3	5,656	9.0

This difference between private and ward practice in an elective procedure is most fortunate for the purpose of this study for it gives an opportunity to test the effect of uterine stimulation on infant mortality in nearly pure culture. This will be discussed in detail in the tables to follow.

Table III shows considerable variation in the use of Pitocin for induction between the various cooperating services. This clearly reflects a broad difference in attitude regarding induction of labor as an elective procedure. Induction was carried out in 11.6 per cent of patients in one hospital, while in another but 0.1 per cent were so treated.

TABLE III. INDUCTION. DISTRIBUTION BY HOSPITAL AND SERVICE STATUS

HOSPITAL	PER CENT LABOR INDUCED		TOTAL
	PRIVATE	WARD	
Beth El	12.7	3.4	11.6
Johns Hopkins	0.1	0.1	0.1
University, Baltimore	0.2	0.1	0.1
Sinai, Baltimore	2.8	0.7	2.1
Kings County		0.4	0.4
Long Island College	8.2	3.1	6.4
Grace-New Haven	3.7	1.8	3.1
Cumberland		0.5	0.5
Colorado General	1.3	0.2	0.2
Sinai, N. Y.	0.2	0.2	0.2
Total number	959	203	1,162
Total per cent	3.9	0.5	1.8

The infant mortality in elective induction for infants alive at the onset of labor and weighing more than 1,000 grams is shown in Table IV. Although the loss rates for premature infants are naturally higher than for term, there were but 44 such infants with a loss of only 2. These might be considered errors in judgment, for one would not electively terminate a pregnancy prior to term. However, the infants were all in the heavier weight group as the low perinatal loss rate of 4.5 per cent attests. The 0.9 per cent rate for private patients is significantly lower than that of 3.8 for the ward. This social difference in infant mortality is present in all the analyses to be presented with the single exception of indicated induction. The reason for this is by no means clear, but it is always apparent in other widely differing studies where social and economic states have been considered. The offspring of the presumably well fed are better protected during labor than those of their less fortunate sisters. As far as the non-whites are concerned, the converse is true once the infant is born alive.

TABLE IV. ELECTIVE INDUCTION
Per Cent Incidence of Perinatal Loss by Service Status and Maturity*†

	PRIVATE	WARD	TOTAL
Premature	3.0	8.3	4.5
Mature	0.8	3.3	1.2
Total	0.9	3.8	1.3

*Infants over 1,000 grams; fetal heartbeat present at onset of labor.
†Toxemia and hemorrhagic complications excluded.

The perinatal mortality rates for patients with indicated inductions are seen in Table V. As would be expected, both the over-all loss rate and premature rate are higher here than in the preceding group. The incidence of prematurity in indicated inductions is 23 per cent as against 4.5 in the former. This accounts for the high over-all rate, and is easily understandable on consideration of the indications for induction.

TABLE V. INDICATED INDUCTION
Per Cent Incidence of Perinatal Loss by Service Status and Maturity*

	PRIVATE	WARD	TOTAL
Premature	16.7	14.3	15.6
Mature	0.0	0.0	0.0
Total	3.1	3.4	3.2

*Infants over 1,000 grams; fetal heartbeat present at onset of labor.

TABLE VI. ELECTIVE ACCELERATION
Per Cent Incidence of Perinatal Loss by Service Status and Maturity*†

	PRIVATE	WARD	TOTAL
Premature	4.6	10.0	5.8
Mature	0.5	2.2	0.7
Total	0.6	2.9	1.0

*Infants over 1,000 grams; fetal heartbeat present at onset of labor.
†Hemorrhagic complications excluded.

The perinatal mortality in elective acceleration in 3,508 cases is shown in Table VI. There were 204 premature infants in this group with a loss rate of 5.8 per cent. Obviously they were heavier premature infants; and because of this and their small number, the over-all rate is but little affected. This latter

figure of 1 per cent with the remarkably low figure of 0.6 per cent on the private services is well within the basic rate.* The ward rate is again higher although the number of such patients is but a small fraction of the total. It is unlikely that anyone will ever set up a control series by arbitrarily accelerating labor in normal women. The low over-all loss rate in this group where no gross indication for acceleration appears seems to answer, in a fairly satisfactory manner, the relationship of Pitocin stimulation to infant mortality.

The perinatal loss rate in 136 indicated accelerations (Table VII) is expectedly high (25 per cent), for this group is composed almost entirely of cases of abruptio placentae. There is here also a higher ward loss rate.

TABLE VII. INDICATED ACCELERATION
Per Cent Incidence of Perinatal Loss by Service Status and Maturity

	PRIVATE	WARD	TOTAL
Premature	45.0	54.5	50.0
Mature	6.4	19.4	11.5
Total	17.9	34.0	25.0

Uterine dysfunction includes the formerly termed entities of primary and secondary inertia. It is defined arbitrarily as a delay in the progress of labor of 2 hours or more. A certain amount of judgment is required in making this diagnosis early in labor. In these cases consultation was usually held with the physician in charge.

The frequency of dysfunction for the various services listed according to social status is shown in Table VIII. Unlike the previously cited elective groups, there is little variation in frequency, here, either from institution to institution or between ward and private services. This lack of variation also speaks well for the uniformity of the diagnostic procedure.

TABLE VIII. INCIDENCE OF UTERINE DYSFUNCTION. DISTRIBUTION BY HOSPITAL AND SERVICE STATUS

	TOTAL DELIVERIES		PER CENT INCIDENCE	
HOSPITAL	NUMBER	PER CENT PRIVATE	PRIVATE	WARD
Beth El	3,411	88.7	4.2	4.7
Johns Hopkins	2,696	25.4	0.7	2.6
University, Baltimore	13,237	36.1	1.1	1.9
Sinai, Baltimore	9,611	65.6	0.5	0.7
Kings County	15,834	0.0		3.5
Long Island College	6,739	64.4	5.8	4.5
Grace-New Haven	1,053	68.8	2.3	3.6
Cumberland	1,467	0.0		1.9
Colorado General	2,430	3.3	1.3	2.1
Sinai, N. Y.	6,798	68.7	0.2	1.4
Total number	63,276	24,600	499	1,039
Total per cent		38.9	2.0	2.7

There are four major techniques by which dysfunction can be treated as indicated by the headings in Table IX. These are (1) Pitocin, (2) Pitocin plus section, (3) section, (4) other. In the grouping here employed, if a patient were given successively enemas, rupture of membranes, and Pitocin, she would fall into the Pitocin group. If the Pitocin were omitted, and cesarean section was performed after the two relatively minor procedures, she would fall into

*Basic perinatal mortality rate is defined as the total infant loss rate of an adjusted population of normal women who have normal term deliveries of infants alive at the onset of labor. This concept will be further developed in future studies of the cooperative material.

the section group. Only if she were neither given Pitocin nor delivered by section would she be classified under other. In this grouping the "Pitocin failures" come under the heading "Pitocin and section," while patients with contracted pelves for whom the simple methods did not achieve results are found in the section group.

TABLE IX. UTERINE DYSFUNCTION. METHOD OF THERAPY AND SERVICE STATUS

SERVICE	PITOCIN		PITOCIN AND SECTION		SECTION		OTHER		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Private	338	67.7	44	8.8	35	7.0	82	16.4	499	100
Ward	474	45.6	33	3.2	120	11.5	412	39.7	1,039	100
Total	812	52.8	77	5.0	155	10.1	494	32.1	1,538	100

Of the 1,538 mothers with uterine dysfunction, 889, or 57.8 per cent, were treated with Pitocin. In 77 of these, or 5.0 per cent, Pitocin failed to affect progress to such a point that easy delivery could be achieved and section was resorted to. This failure rate is about one half that cited in previous work with intermittent intramuscular Pitocin.

The private physician resorted to cesarean section after Pitocin more than twice as frequently as the ward doctor. On the other hand section was more frequently the primary means of treatment on the wards. These data do not permit any factual conclusions to be drawn from this difference, but one might surmise a rightful reluctance on the part of the private physician to continue Pitocin therapy for too long a time; while on the other hand the ward physician is more frequently confronted with contracted pelves which should contraindicate its use.

The frequency of cesarean section was 14.5 per cent, not an excessive figure considering the seriousness of the complication. Section was used without Pitocin in 10.1 per cent of patients.

Other methods of therapy such as watchful waiting, enemas, and rupture of membranes were employed in 32.1 per cent of patients with dysfunction.

The perinatal mortality rate with this complication, shown in Table X, is gratifyingly low. An over-all rate of 3 per cent in face of one of the most serious complications of labor reflects real progress in knowledge and treatment of this abnormality. The similarity of the loss rates under the four main headings is an indication of seasoned obstetrical judgment. The low rate of

TABLE X. UTERINE DYSFUNCTION
Per Cent Incidence of Perinatal Loss by Method of Therapy, Service Status and Maturity*

	PITOCIN	PITOCIN AND SECTION	SECTION	OTHER	TOTAL
Private.—					
Premature	14.3	100.0	0.0	0.0	13.6
Mature	1.2	2.3	0.0	1.3	1.3
Total	1.8	4.5	0.0	1.2	1.8
Ward.—					
Premature	2.6	0.0	0.0	12.0	5.5
Mature	3.8	3.2	2.7	3.4	3.5
Total	3.7	3.0	2.5	3.9	3.6
Grand total	2.9	3.9	1.9	3.5	3.0

*Infants over 1,000 grams; fetal heartbeat present at onset of labor.

3.9 per cent in the Pitocin failure group can be compared with the older figure of nearly 20 per cent. This indicates a realization that once Pitocin has failed to achieve progress quickly, cesarean section must be resorted to promptly if the infant mortality is to be kept low.

There were no maternal deaths among the 5,656 patients in this series who received Pitocin.

There was one ruptured uterus as follows: The patient was a white 31-year-old para i-o-i-i who had been given Pitocin with her previous term delivery because of uterine dysfunction. Her x-ray pelvimetry showed an entirely normal pelvis. She went into labor spontaneously at term, and after 13 hours and 45 minutes the placenta separated spontaneously and the fetal heartbeat disappeared. At this time it was discovered that she had a compound presentation with both vertex and hand presenting. She was given one transfusion, and labor was stimulated with the usual dosage of dilute intravenous Pitocin. After 2 hours of stimulation the uterus ruptured and she was then delivered abdominally of a stillborn 3,350 gram infant that lay free in the abdominal cavity. The delivery was followed by hysterectomy. The patient survived.

Perhaps Pitocin stimulation was unwise in this instance because of the compound presentation. Nevertheless, one ruptured uterus in this large series is not above the expected rate in patients receiving no Pitocin.

The one other complication frequently suspected in association with Pitocin stimulation is postpartum hemorrhage. The over-all incidence of 4.8 per cent, shown in Table XI, does not confirm this suspicion. Even on a breakdown into separate categories, the incidence of postpartum hemorrhage is elevated only where the stimulation was indicated by a hemorrhagic complication.

TABLE XI. INCIDENCE OF POSTPARTUM HEMORRHAGE IN 5,656 DELIVERIES WITH PITOCIN BY SERVICE STATUS

	PRIVATE	WARD	TOTAL
Induction, elective	2.6	4.8	2.9
Induction, indicated	6.5	19.7	11.7
Acceleration, elective	3.0	6.3	3.5
Acceleration, indicated	11.1	25.0	17.6
Dysfunction	6.0	10.5	8.5
Total	3.4	9.4	4.8

We have not attempted to draw any conclusions from these data for they appear to speak for themselves. They represent current practice in the use of intravenous Pitocin in the ten hospitals under consideration. There is no information available regarding its use on a national scale, but one might hazard a guess that the frequency figures here presented are an underestimate.

We wish to express thanks to the following Chiefs of Service of the cooperating hospitals:

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Discussion

DR. J. L. REYCRAFT, Cleveland, Ohio.—In dealing with mass statistics, many of the interpretations must be based on broad assumptions. Thus the author says: "These might be considered errors in judgment, for one would not electively terminate a pregnancy prior to term." And again: "It is unlikely that anyone will ever set up a control series by arbitrarily accelerating labor in normal women." Perhaps not for the purpose of establishing a control series, but for other reasons, there is little doubt that Pitocin is today being administered on occasion to women who are laboring normally.

In general, this paper presents us with the picture of what is happening, or has been happening in 10 major institutions. As a piece of reporting it has merit and interest. It cannot be implied that, because they are frequent, these various uses are good. And the impersonal

statistics always leave us with some personal questions. Thus, for example: How many of the women with uterine dysfunction were first treated by some other means? This might influence our decision when facing an individual case.

We all are conscious of the efficacy of the use of intravenous Pitocin infusions when properly supervised. However, we must not forget that there have been other agents and techniques which have been of great value. For many years, we gave intravenous glucose alone as a means of stimulating labor in cases of beginning exhaustion. Also, we have all seen the value of the judicious use of opiates, especially morphine sulfate.

The role of amniotomy as a means of induction of labor or to accelerate labor is always important. Three years ago, I reported a series of 500 such cases from my own practice, at the meeting of the American Academy of Obstetrics and Gynecology, in which I purposely never used Pitocin. It was noted that the latent period was not unduly long in most instances and that the end results were excellent. There were no maternal deaths and the corrected fetal mortality was 0.04 per cent.

Mauzy has shown us that Pitocin can be utilized to induce labor in toxemic patients with safety, and most of us use it routinely following delivery with dependable results.

As many authors have noted, it is customary to give 1 c.c. of Pitocin in 1,000 c.c. of 5 per cent dextrose in water or normal saline, and the speed of administration is governed by the response of the uterus. This applies to its use for induction or usually during labor.

It is one of the most potent medications available, and is largely free of vasopressor activity. The latent period is greatly shortened, and there is no question that it has taken its place for all time in the armamentarium of the obstetrician. We are all pleased to have heard this statistical presentation of the use of Pitocin-1955.

DR. WILLIS E. BROWN, Little Rock, Ark.—One of the characteristics of the American scene is the rapid change of pattern, the wide swings of the pendulum. This is manifest in both the frivolous and the serious, being evident in the styles of our clothes, design of houses, politics, size of families and many other facets of life. While disillusioning, it is not surprising to find this national characteristic coloring even our scientific endeavors—even medicine—even obstetrics, the oldest of the healing arts.

This excellent report by Dr. Hellman and his associates depicts the third arc of the oxytocic pendulum and portends the median of sound clinical practice. Pituitary extract is not the first, and I am afraid not the last, modality of clinical practice to be prematurely banished as unrestrained enthusiasm encourages its indiscriminate employment.

Proper clinical perspective in the use of pituitary extracts in obstetric practice has been difficult to obtain. When first introduced, Pituitrin was an impure and poorly standardized product. It contained excessive amounts of protein, was heavily contaminated with vasopressin, and was of variable oxytocic potency. Despite these problems, the early use was rewarded by dramatic results which were enthusiastically reported and led the inexperienced to use it indiscriminately in any and all tardy and prolonged labors. Various complications, coupled with the frequent vasospasm and death from cardiac complications, brought this potentially useful agent to an ignominious and premature banishment.

Slowly, as this report attests, both the agent and our clinical judgment have been refined. One can hope that the publication of this *very proper* report does not precipitate a resurgence of ineptitude as the uninitiated resume the uninhibited exploitation of this useful agent.

We, too, have employed this modality in the practice of obstetrics and as we have gained experience our results have been excellent. Our exercise of judgment and caution has resulted in our formulating the following rules for its use:

1. A physician must personally prepare and begin the infusion, and
2. He must remain with the patient while the infusion is running. (The nurse is instructed to clamp off the tubing if the physician leaves the labor suite.)

These two simple rules, amplified in some details, will not prevent all accidents. They do require that a physician be present in the labor room and take a personal role in this activity of Pitocin infusion—whether induction or augmentation. We have observed that even the most casual and harassed of attendants will assume responsibility and exercise reasonable judgment and clinical control under these circumstances.

This has been an excellent paper, establishing by statistics the variety of our clinical impressions. These results are from "university or teaching hospitals," and reflect the firm hand of matured clinical judgment. I urge the exhibition of a series of safety regulations, lest the casual reader misinterpret the *real* source of these good results, namely, good clinical control, for I am convinced that under other circumstances great damage might result. Unless the "routine" of the university hospitals is transposed to the less well-regulated institutions, this useful agent will again become stigmatized to the detriment of mothers.

DR. J. BAY JACOBS, Washington, D. C.—There are some unfavorable results that are not reported and do not come to our attention. There are a certain number of ruptured uteri, possibly some fetal losses, and yet we do not hear about hem.

In past years I have used divided doses of Pituitrin or Pitocin to induce labor or treat inertia, and have always realized that their use should be attended by some degree of concern. The individual physician must stay around and watch the patient himself and not trust anybody else's judgment. He should check the fetal heart frequently, and note the character, duration, and frequency of contractions.

I have observed that where broken doses of Pitocin or Pituitrin were given, the uterine contractions, although they appeared effective and rhythmic, frequently did not produce the cervical dilatation that occurs in normal labor, or that one might note with the use of Pitocin drip. Pitocin drip in that respect I would say is much more reliable. It produces a more uniform type of uterine stimulation and contraction, resembling the institution of physiologic labor.

I was also impressed with the statement of Dr. Reycraft that in his large series of inductions he found it unnecessary to administer any oxytocic. A similar situation obtains in my series. If the patient is ready for labor to be induced and there is no contraindication, it is hardly necessary to use oxytocics. Within a reasonable time after the membranes are ruptured, possibly within an hour or so, the patient will start in labor and be delivered in a few hours.

The use of Pitocin should be limited, as well as rupture of the membranes of course, to those whose judgment in obstetrics is recognized. The hospital should be very careful in permitting individuals to induce labor by either, or by the combined procedures.

In regard to the relationship of incidence between house and private cases, I am inclined to think that the private physician pays a little more attention to his own case than he does to house cases. Then again, there is a tendency to be more concerned in training residents and, for that reason, Pitocin would naturally not be used as often.

This is an excellent procedure to use when conditions appear favorable, but I think that its use should be highly restricted and that even the obstetrician with good judgment should resort to oxytocics only when indicated.

DR. R. GORDON DOUGLAS, New York, N. Y.—I want to say just a very few words concerning what may be considered a very minor detail, namely, the amount of this very active principle employed. Dr. Hellman has referred to a dosage of 1 c.c. Our literature is filled with references to dosage in minims and other volumetric measurements. We are dealing with an extraordinarily active principle—1/1,000 mg. of which will produce a measurable clinical effect.

We are currently using a preparation that contains one unit per cubic centimeter. It is true that most commercial material has 10 units per cubic centimeter; however, this situation may not continue indefinitely. Why not be definitive, as with most other medications, be specific and define the dosage we use in units rather than meaningless terms?

DR. J. P. GREENHILL, Chicago, Ill.—Dr. Hellman said he did not believe anyone would have the temerity to use pituitary extract routinely in a large series of women who were having normal labor. One of our guests of last year, Louros of Athens, reported on 10,000 cases of what he called "accelerated delivery." The acceleration was brought about by a combination of Demerol and an oxytocic and the results were excellent. In spite of the good results reported by enthusiasts of the use of pituitary extract, I should like to stress that pituitary extract is a dangerous drug.

Regardless of all the rules we make for its use, trouble will arise in an occasional case, particularly in small hospitals where there is limited personnel. In my opinion whenever pituitary extract is given either intramuscularly or intravenously, a physician should be with the patient all the time and should watch the effects of the drug constantly.

DR. FREDERICK J. HOFMEISTER, Milwaukee, Wis.—As a practitioner I would like to emphasize the fact that we, as specialists, are setting a pattern which is followed by the country doctor. In our own state of Wisconsin in a period of twelve months, of 26 maternal deaths, 15 were due to ruptured uteri associated with the administration of Pitocin in intravenous drip or fractional doses. I think that is what we must remember when we create a pattern. In well-controlled hospitals with well-regulated services, I think this procedure is all right, but we must think of the over-all picture of obstetrics in America when we make statements that are grasped so readily by the general practitioners who do the greater proportion of the obstetrical work.

DR. HELLMAN (Closing).—I want to point out that one of the things which goes to make the cooperative study a success is the lack of expression of opinion by people who use the data. The reports must be factual.

It is interesting that Dr. Reycraft picked up the two sentences to quote upon which I worked hardest. What I meant by the administration of oxytocics electively as an experiment was that nobody would set up such an experiment with adequate controls. My objection of Dr. Louro's paper and the reason I did not mention it was that it had no controls and nobody has any idea what would happen to patients in Athens whose labor he did not stimulate.

I think Pitocin is a dangerous drug and its use should be surrounded by some aura of respect. If it is, maybe it will be used more carefully and, as far as I am concerned, anyone who says "We Pitted the patient," or "We used Pit," is guilty not only of poor English but of too great familiarity.

With regard to Dr. Douglas' comment as to units, I would like to explain that in our printed paper the units are given in addition to cubic centimeters. I hope that some day we will be able to talk of this in micrograms, etc.

Dr. Brown's statement about abuse of this drug is again correct. I hoped that this point would be made in the discussion because I did not think it was part of a statistical report. In this regard I want to say one more thing. There is a factor which we cannot evaluate in the use of this drug electively, either to accelerate labor or to induce labor. This concerns damage to the babies that do not die. I have no data on this and I do not think anybody else has, but I would like to call your attention to the fact that somewhere between 5 and 7 babies per 1,000 have some sort of central nervous system damage. Whether this drug has any relationship to this sort of damage or not, I do not know. It will take a great number of years and some very careful study perhaps of this sort to find it out.

URETHROVESICOPUBIC RELATIONSHIPS IN THE FEMALE*

2. Effects of Coitus, Parturition, Menopause, and Uterine Suspension

C. PAUL HODGKINSON, M.D., DETROIT, MICH.

(From the Department of Gynecology and Obstetrics, Henry Ford Hospital)

VARIABLE degrees of lasting attenuation, relaxation, and other sequelae of trauma are hallmarks of parturition in the birth canal.[1-5] By modern obstetrical standards, they signify the ransom price of pregnancy. How, and to what possible end, these changes affect the urethrovesicopubic relationships are questions which have fired the imagination of gynecologists for years.[6-13] Of more fundamental importance are the subtle changes in urethrovesicopubic relationships which develop in married nonparous women as they approach and transcend the menopause. The comparison and demonstration of changes in urethrovesicopubic relationships by these influences are the intent of this study.

The comparative material was selected from case studies of over 300 patients. The procedure of investigation was standardized to include: detailed history, complete general physical examination, gynecological, and sometimes urological examination, routine laboratory studies, cystometric evaluation, and urethrocystograms by the metallic bead chain technique.[14, 15] Five groups of patients were compared.

Group 1 consisted of 5 nonparous patients ranging from 14 to 48 years. The youngest patient was virginal. The others had been married for periods ranging from two months to eight years. None of the patients in Group 1 admitted or demonstrated physical evidence of having been pregnant.

Group 2 included 2 patients who had delivered vaginally at least one full-term infant. Neither patient had evidence of uterovaginal prolapse. Both were without gynecological and urinary symptoms.

The patients in Group 3 all demonstrated uterovaginal prolapse as sequelae of parturition.

Group 4 patients were classified according to the common symptom: urinary stress incontinence. They may or may not have demonstrated anatomical weakness.

Group 5 was composed of 2 patients who complained of urinary stress incontinence secondary to Gilliam-Doléris uterine suspension. One was relieved of symptoms by hysterectomy and the other by pregnancy and vaginal delivery. Considerable alteration in urethrovesicopubic relations was observed in each patient. Urethrocystograms, by the metallic bead chain technique, permitted accurate and undistorted anteroposterior and lateral radiograms. All radiograms were exposed with the patient standing erect.

The first anteroposterior-lateral set, designated "nonstraining," was taken with the patient at rest, and the second, "straining," was taken with

*Presented at the Sixty-seventh Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Va., Sept. 6 to 8, 1956.

the patient straining downward. Voiding studies were not performed nor were they considered pertinent to a study intended to evaluate the effects of coitus, parturition, menopause, and uterine suspension upon urethrovesical support.

Results

Group 1. Nonparous Group.—The age and marital status of the patients in Group 1 are shown in Table I. Nonparity was their common qualification. All patients were experiencing normal menstrual function except for Patient 5 who had had menopausal amenorrhea for two years.

TABLE I. GROUP 1.

PATIENT NO.	AGE	MARITAL STATUS
1	14	Virgin
2	19	Married, 2 months
3	23	Married, 2 years
4	34	Married, 6 years
5	48	Married, 4½ years

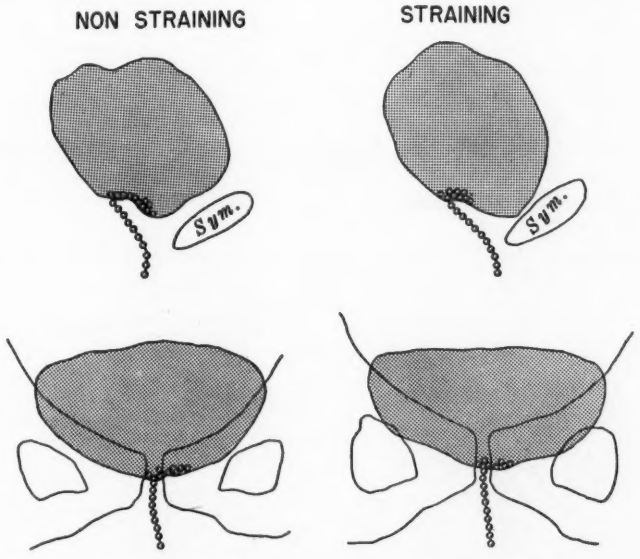

Fig. 1.—Patient 1 (A. Z., 504217). Aged 14 years. Typical urethrocystogram of normal virgin.

Comparative study of the urethrocystograms of the normal patients included in Group 1 was intended to demonstrate variations in urethrocystopubic relationships as influenced by coitus, increasing age, and menopause.

Because the urethrocystograms of Patients 1, A. Z. (Fig. 1), Patient 2, J. S. (Fig. 2), and Patient 3, M. T. (Fig. 3) demonstrated acceptable similarities, it was convenient to compare them collectively.

The "nonstraining" anteroposterior radiograms showed the urethra and bladder to be in the midline with the lowest bladder level midpubic. The lateral urethrovesical angles were symmetrical and averaged somewhat greater than 100 degrees.

Straining caused slight flattening of the bladder dome with lateral extension of the sides. Descent of the bladder base and the urethra was minimal.

The lateral "nonstraining" radiograms showed the anterior one third of the bladder to be located suprapubically. A clear space could be visualized between the bladder and the pubis. The urethra joined the bladder at a point posterior to the midcoronal bladder plane. The urethral catenary was straight until the distal end where it arched downward. The anterior urethrovesical angle was acute while the posterior urethrovesical angle was obtuse.

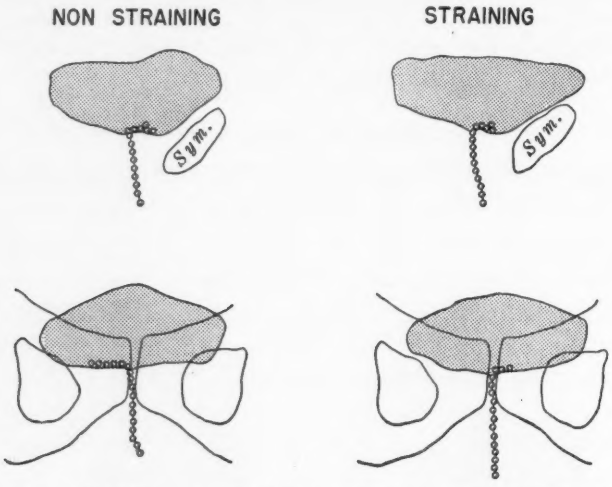

Fig. 2.—Patient 2 (J. S., 811836). Aged 19 years, para 0. Urethrocystogram after 4 months of marriage.

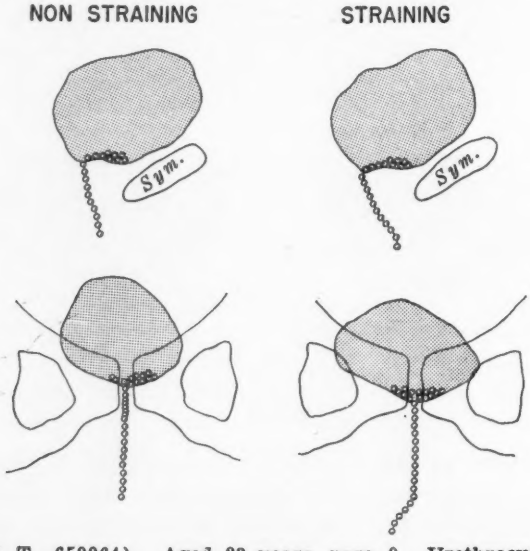

Fig. 3.—Patient 3 (M. T., 659064). Aged 23 years, para 0. Urethrocystogram after 2 years of marriage.

Straining caused only the slightest variation in urethrovesicopubic relationships. The general location of the bladder and urethra appeared to be unaltered. Close scrutiny of the lateral radiograms disclosed diminution or obliteration of the clear vesicopubic space which was caused by anterior rotation of the bladder. As the result of this action the anterior urethrovesical angle was made more acute while the posterior angle tended to be somewhat more obtuse.

Patient 4, M. L. (Fig. 4), was 34 years of age and was barren after having been married six years. The "nonstraining" anteroposterior and lateral radiograms disclosed normal urethrovesicopubic relationships. The straining effort resulted in descensus of the lowermost bladder border which was shown to be caused mainly by deficient posterior support. Rather than rotated anteriorly the bladder appeared to be compressed downward in a vertical direction. This was maximum posterior to the urethrovesical junction. Thus, the vesicopubic space was obliterated and the anterior and posterior urethrovesical angles made more acute.

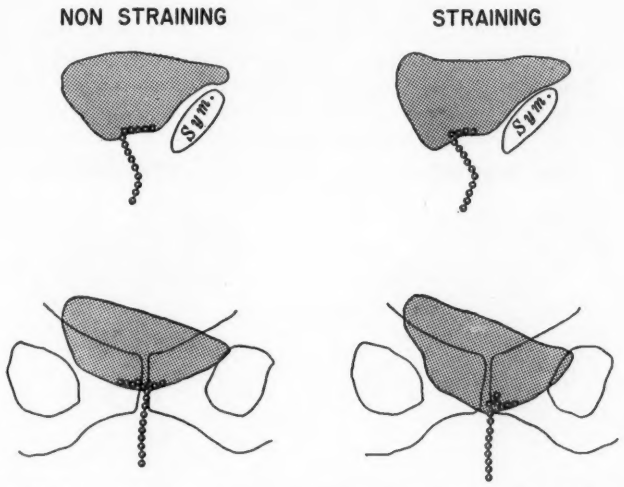

Fig. 4.—Patient 4 (M. L., 817488). Aged 34 years, para 0. Urethrocystogram after 6 years of marriage.

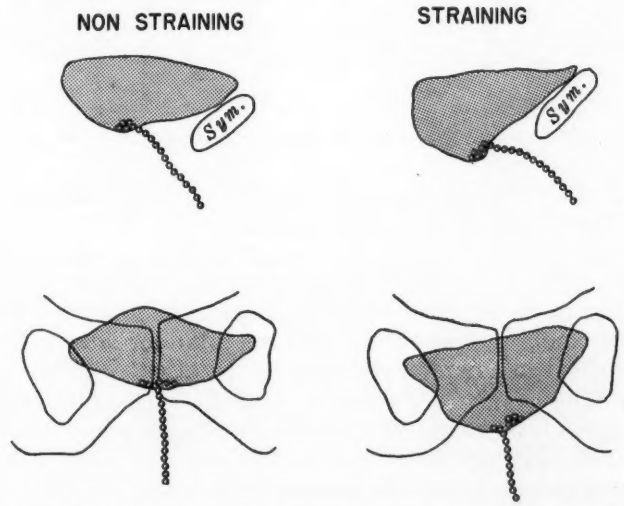

Fig. 5.—Patient 5 (J. S., 818727). Aged 48 years, para 0. Urethrocystogram 2 years after menopause.

Patient 5, J. S. (Fig. 5), was 48 years of age, had been married four and one-half years, and was two years postmenopausal. The "nonstraining" radiographs showed normal urethrovesicopubic relationships. As with Patient 4, straining caused bladder descensus, maximal posteriorly. The deficient

posterior support was increased and partial rotation of the posterior urethrovesical angle occurred. This converted the nonstraining posterior urethrovesical angle into a less obtuse angle. The general bladder descensus caused obliteration of the vesicopubic space and more acute anterior urethrovesical angulation.

In summary, Group 1 patients demonstrated occasional minor changes in urethrovesicopubic relationships. Relaxation of the urethrovesical support appeared to be mildly progressive with increasing age and presumably should be considered as a normal variation for the nonvirginal female.

Group 2. "Normal" Parous Patients.—The "normal" parous patient was defined as one who had been delivered vaginally of at least one full-term infant and who demonstrated, upon vaginal examination, minimal degrees of asymptomatic vaginal attenuation, relaxation, and other sequelae of trauma. Two patients were selected.

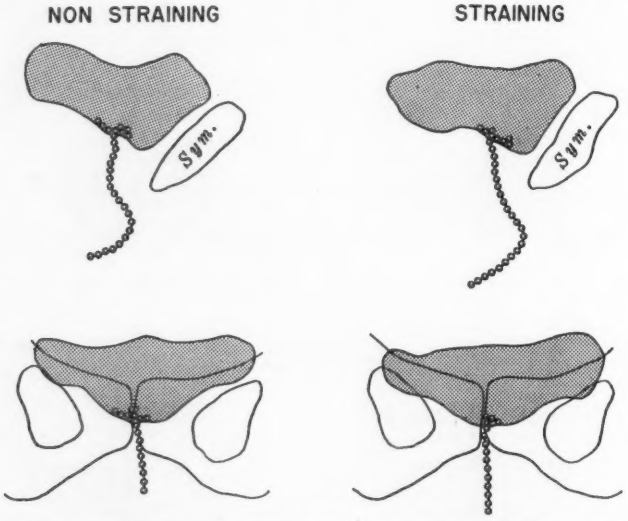

Fig. 6.—Patient 6 (J. D., 723901). Aged 36 years. Urethrocystogram in normal multipara.

Patient 6, J. D. (Fig. 6), aged 36, mother of two children, was admitted to the hospital for biopsy of cervical erosion.

Although the urethrovesicopubic relationships as demonstrated in the "nonstraining" and "straining" anteroposterior radiograms compared favorably with standards established from normal patients of Group 1, minor variations in the configuration of the inferior bladder silhouette were evident and will be described in common with those of Patient 7 (Fig. 7).

The lateral radiograms of Patient 6 (Fig. 6) showed the suprapubic vesical segment to be well maintained. The urethrovesical junction was in normal position in its relationship with the pubis, and the anterior and posterior urethrovesical angles conformed to normal standards.

The posterior bladder segment was elongated in the backward direction. This circumstance caused the relative position of the urethrovesical junction to be located in the midcoronal bladder plane. This gave the specious impression that the urethra was displaced forward.

Patient 7, V. E. (Fig. 7), aged 34, was the mother of two children. The anteroposterior urethrovesicopubic relationships of Patients 6 and 7 showed common variations in the integrity of the support to the bladder floor.

Close inspection disclosed a minor symmetrical deformity in the silhouette of the inferior bladder. Here the uniform curve of the bladder base was replaced by a shallow bilateral sigmoid graduality with the declivity segment directed medially. This suggested preservation of lateral support and partial failure of medial bladder support. The lateral support appeared to conform to the location of the pubococcygeus muscle.

The lateral urethrocystograms of Patient 7 (Fig. 7) showed the urethrovesical junction to be located in the midcoronal plane. The entire bladder was retrocessed thereby decreasing the suprapubic bladder segment. A minor degree of downward and backward rotation of the bladder was evident from observation of the lateral radiographs taken during the straining effort.

In Patient 7 (Fig. 8), close scrutiny of the immediate posterior urethrovesical area in the "straining" radiogram disclosed evidence that the degree of obtuseness of the posterior urethrovesical angle had been considerably lessened as the result of the posteroinferior rotatory action. The anterior urethrovesical angle remained acute.

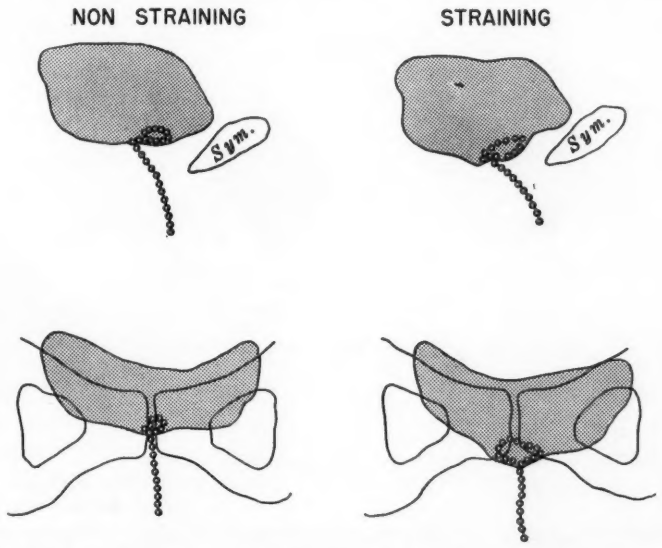

Fig. 7.—Patient 7 (V. E, 551409). Aged 34 years. Urethrocystogram in normal multipara.

In summary, the least demonstrable effects resulting from parturition upon urethrovesicopubic relationships could be ascribed to weakening of bladder support in the posterior and the central inferior areas. In Patient 6 elongation of the posterior bladder segment occurred, while Patient 7 demonstrated evidence of retrocession of the entire bladder. In both patients, minor grades of deficiency of central inferior support were evident. The integrity of the lateral inferior support resulted from efficient pubococcygeal muscles.

Group 3. Uterovaginal Prolapse.—The urethrovesical relationships of uterovaginal prolapse have been previously characterized as downward and backward rotation of the bladder with assimilation of the urethrovesical junction into the anterior bladder wall.[14-15] These features vary in degree and are not consistently related to the obstetrical history. The comparative degree of downward and backward rotation of the bladder with uterovaginal prolapse are illustrated in the "nonstraining" and "straining" lateral urethrocystograms of four patients shown in Figure 8.

The urethrovesical angles were found to vary according to the degree, phase and type of the prolapse. During the straining phase, the posterior urethrovesical angle tended to become more acute, but its measurement was beclouded with difficulties. The urethral catenary often described an arc which blended with the posterior bladder wall, rendering its measurement as an angle impossible. The anterior urethrovesical angle usually remained acute.

Further experience has demonstrated that bladder prolapse may be complete or partial.

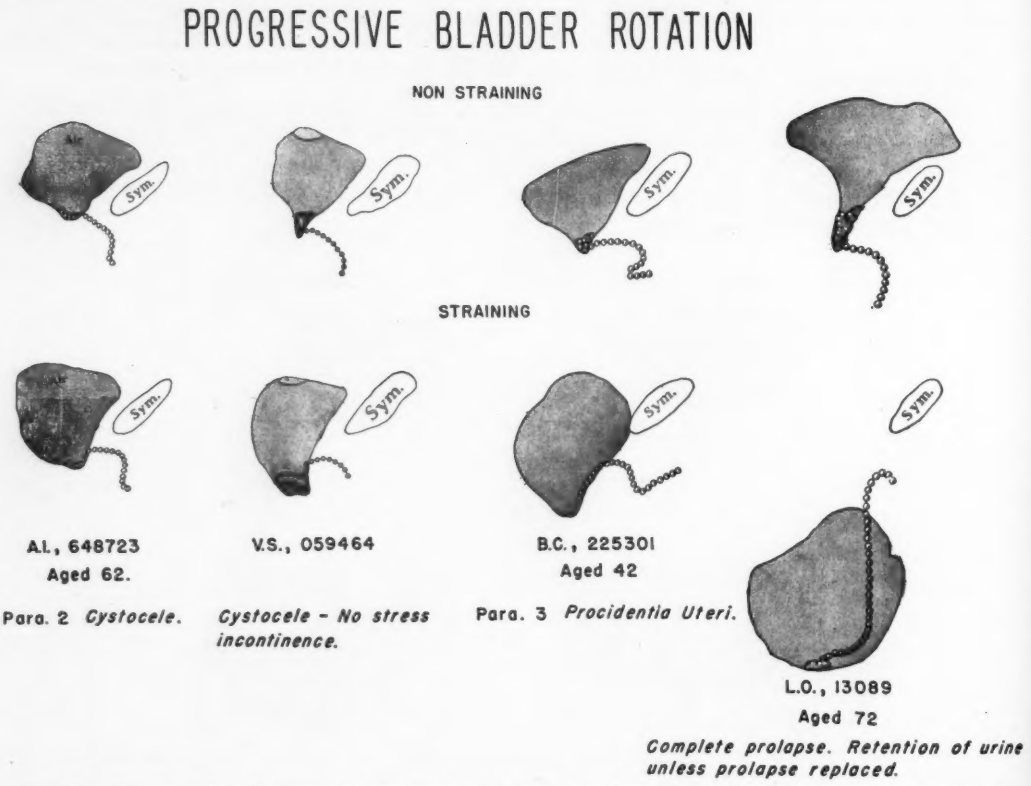

Fig. 8.—Comparative degree of downward and backward rotation of bladder in urethrovaginal prolapse.

Patient 8, E. B. (Fig. 9) aged 58, was the mother of four children. Clinical examination disclosed an extensive uterovaginal prolapse, and pathological obesity. Preoperative urethrocystograms revealed the bladder prolapse to be partial or segmental.

The anteroposterior "nonstraining" urethrocystograms showed the bladder to be dumbbell shaped in the vertical direction with the superior bulb larger than the inferior bulb. The superior bladder bulb occupied the position of the normal bladder and appeared to rest upon constricting lateral supports which corresponded in location to the pubococcygeal muscles. In addition to augmented bladder descensus, straining resulted, like the action of an hourglass, in evacuation of the larger superior bladder bulb into the inferior bulb. Thus, the relative size of the superior and inferior bladder bulbs was reversed.

The lateral "straining" urethrocystograms demonstrated the urethra to enter the inferior bladder bulb in a vertical direction at a high point on the anterior bladder wall. Straining caused additional downward and backward bladder rotation.

Patients with uterovaginal prolapse seldom complain of symptoms of urinary stress incontinence. They are generally highly continent and often find it necessary to replace the prolapsed organs to facilitate voiding.

Patients with partial or segmental bladder prolapse sometimes complain of a peculiar type of incontinence which has appeared to be related to sudden change in posture rather than to efforts commonly known to cause urinary stress incontinence. This postural incontinence resulted in loss of urine highly resembling that observed in "incontinence of overflow." Yet these patients were capable of emptying the bladder completely when their prolapsed organs had been replaced. Patients with this type of anatomical defect have a propensity to develop urinary stress incontinence following vaginal plastic operations.

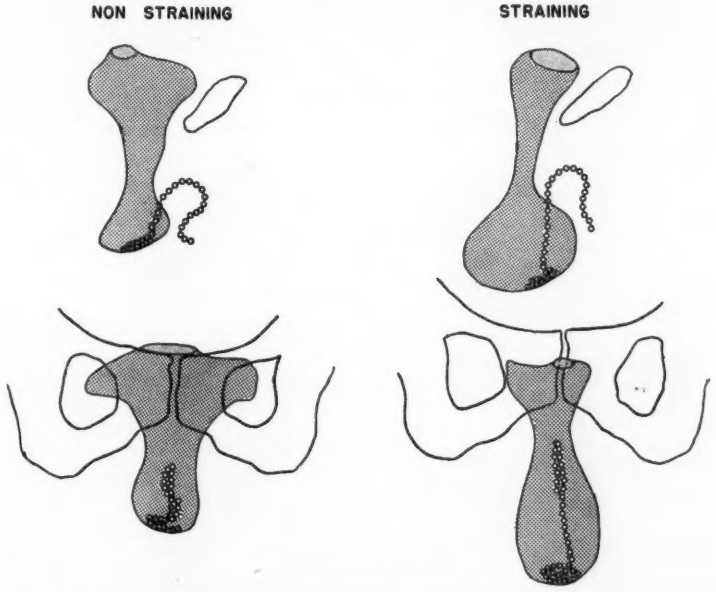

Fig. 9.—Patient 8 (E. B., 767831). Aged 58 years, married, para iv. Urethrocystogram showing segmental prolapse of bladder.

In summary, patients who have uterovaginal prolapse demonstrate varying degrees of downward and backward rotation of the bladder. The bladder prolapse may be complete or partial.

Group 4. Urinary Stress Incontinence.—Urinary stress incontinence in the female has been shown to be associated with anatomical changes characterized by downward vertical thrust of the bladder without rotation and displacement of the internal urinary meatus to the lowermost bladder level.[1, 4, 7, 14, 15] It has not been emphasized that these relationships may be variable in degree and that intensity of symptoms may be maximum in patients who demonstrate minimum gross anatomical changes. Figs. 10 and 11 show the variable degrees of downward displacement observed in Patients 9, D. I. (Fig. 10), and 10, H. G. (Fig. 11), who had severe symptoms of urinary stress incontinence.

Conversely, as uterovaginal descensus increased, stress incontinence was often relieved. Figs. 12, 13, and 14 show urethrocystographic findings of Patient 12, L. L., serially studied at sixteen- and thirteen-month intervals. Amenorrhea of the menopause developed four months prior to the time of the last urethrocystogram. The first urethrocystogram (Fig. 12) was performed in May, 1953. She complained of bothersome, but not embarrassing, symptoms

of urinary stress incontinence. The next urethrocystogram (Fig. 13) was performed during September, 1954, when the symptoms of urinary stress incontinence were unchanged. During 1955 her symptoms spontaneously improved and bothersome urinary stress incontinence became less of a problem. Her last menstrual period occurred in July, 1955. The final urethrocystogram (Fig. 14) was performed in October, 1955. Comparison of the radiograms showed progressively severe bladder prolapse. Although downward and backward rotation of the bladder was not a prominent feature, the

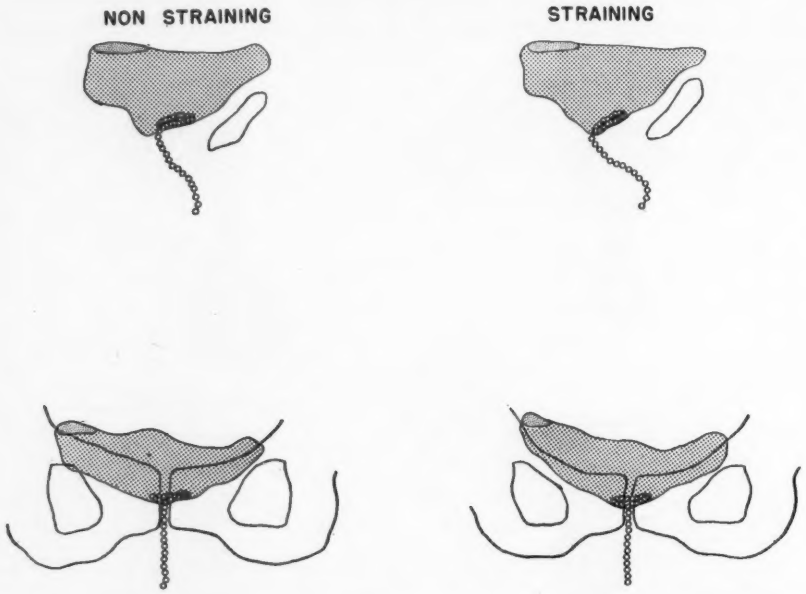

Fig. 10.—Patient 9 (D. I., 668709). Aged 44 years, married, para iii. Urethrocystogram in stress incontinence.

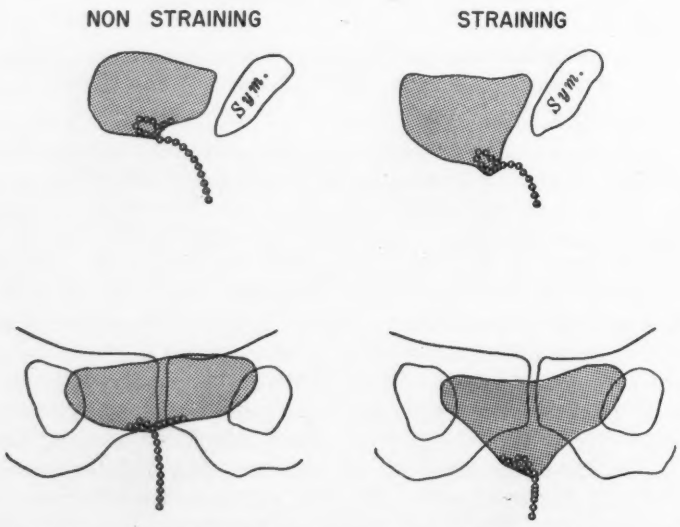

Fig. 11.—Patient 10 (H. G., 680406). Aged 66 years, married, para vii. Urethrogram in stress incontinence.

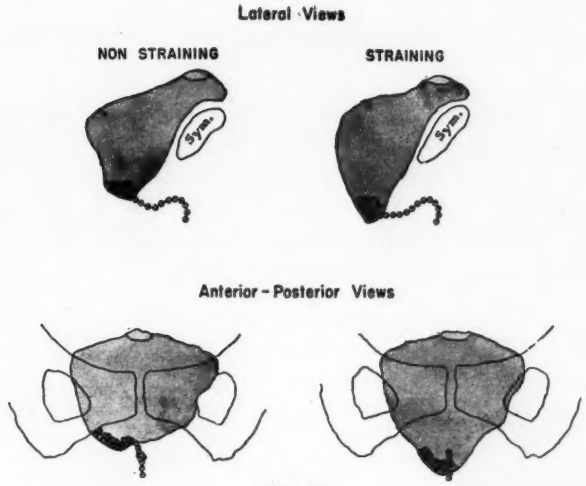

Fig. 12.

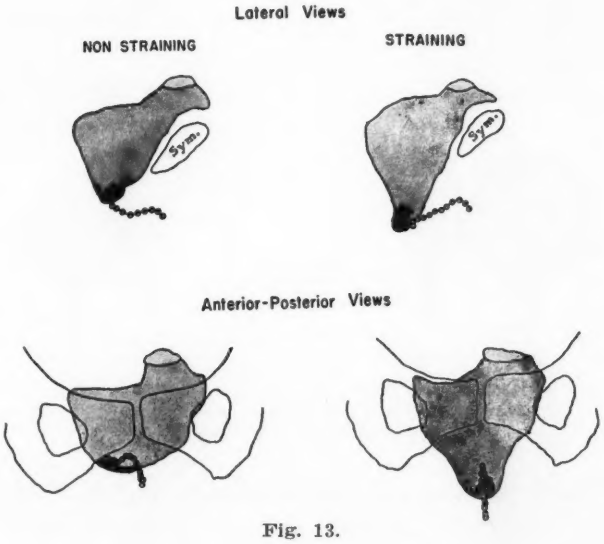

Fig. 13.

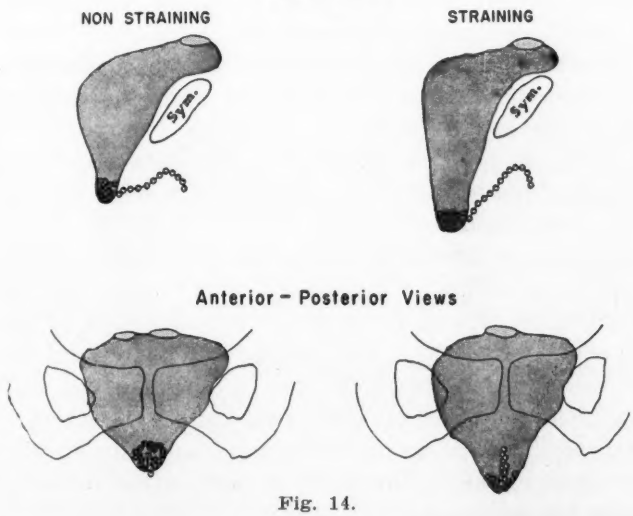

Fig. 14.

Figs. 12, 13, and 14.—Patient 11 (L. L., 153498). Urethrocystograms showing progressive degrees of loss of anatomical support during menopause.

"straining" lateral radiogram taken in October, 1955, showed the urethrovesical junction to be slightly above the lowermost bladder level, and at a level considerably below that of the external urinary meatus. The correlation between the improved symptomatology and the progressive anatomical changes supported the clinical impression that estrogen deficiency may be an important etiological factor in uterovaginal prolapse.

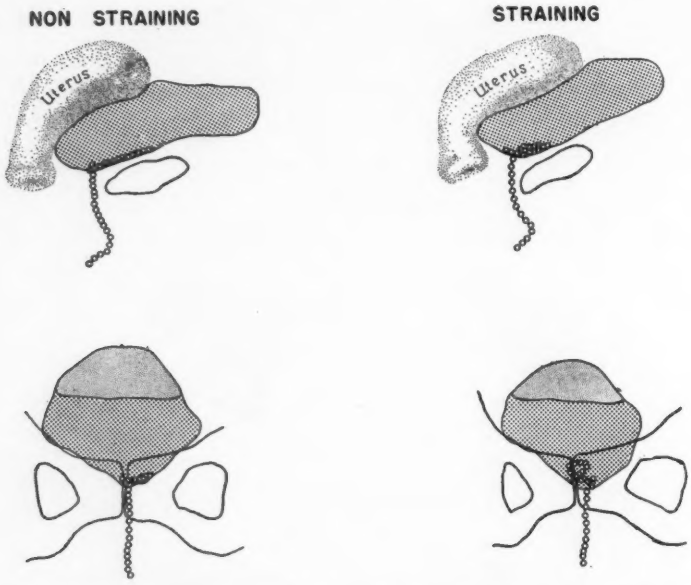

Fig. 15.—Patient 12 (C. E., 130304). Aged 47 years, married, para ii. Urethrocystogram after Gilliam-Doléris uterine suspension.

Group 5. Urethrovesicopubic Relationships and Gilliam-Doléris Uterine Suspension.—The following 2 patients had symptoms of urinary stress incontinence following uterine suspension by the Gilliam-Doléris procedure. Both demonstrated common alterations in urethrovesical relationships which were caused by the technically successful operative procedure. Both were relieved of symptoms of urinary stress incontinence when the constricting influence of the forward-suspended uterus was relieved. The first patient was successfully treated by hysterectomy alone.

Patient 12, C. E. (Fig. 15), aged 47, para ii, demonstrated unusual urethrovesicopubic relationships which were inconsistent with the symptomatology of urinary stress incontinence.

The anteroposterior urethrocystograms demonstrated normal bladder and urethral positions in both "straining" and "nonstraining" radiograms. The lateral radiograms showed far anterior displacement of the bladder with posterosuperior compression from the acutely anteflexed and firmly suspended uterus. From these observations it was the considered opinion that the urinary incontinence was caused by posterosuperior extravesical pressure with diminution and limitation of potential bladder capacity. Abdominal complete hysterectomy was deliberately performed as definitive therapy for the urinary stress incontinence.

The postoperative urethrocystograms (Fig. 16) demonstrated liberation of the posterosuperior bladder with improvement in bladder position resulting from posterior recession. The symptoms of urinary stress incontinence have been completely relieved and nocturia is no longer a problem.

Patient 13, A. G. (Fig. 17), aged 28, was nulliparous when subjected to uterine suspension by the Gilliam-Doléris technique for symptoms sometimes ascribed to uterine retroversion. She developed symptoms of urinary stress incontinence which were refractory to various forms of therapy. When she was first examined in August, 1952, urethrocystograms disclosed urethrovesicopubic relationships similar to those of Patient 12. Reoperation for release of the acute anterior uterine fixation was recommended and refused by the

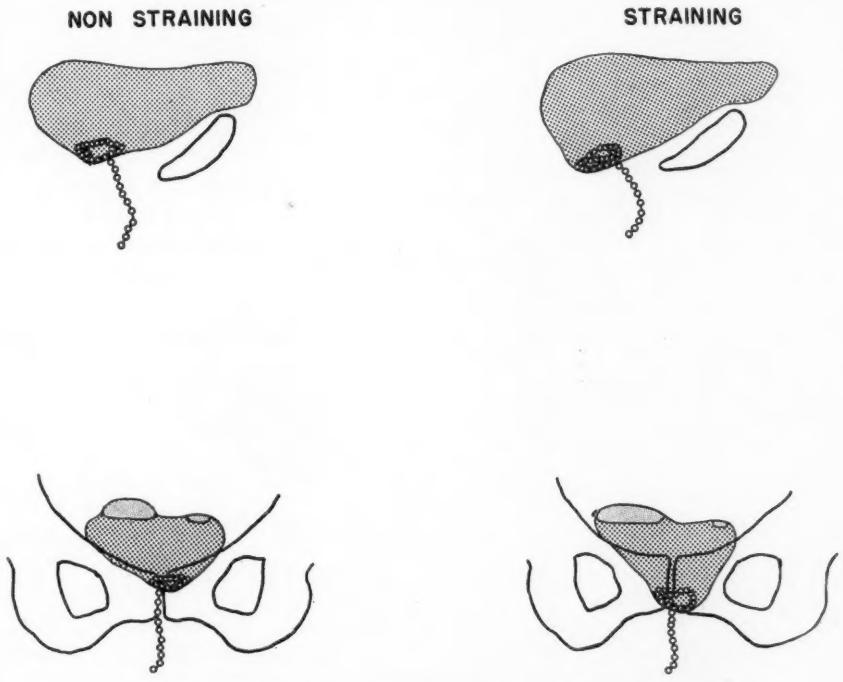

Fig. 16.—Patient 12. Changes effected by hysterectomy.

patient. As an alternative, it was recommended that she become pregnant. Pregnancy was delayed until 1955. She was delivered vaginally of a normal term infant who weighed 3,850 grams. The postpartum urethrocystograms were obtained three months following delivery (Fig. 18).

The restoration toward normal in the urethrovesicopubic relationships has been associated with considerable but not complete relief of the urinary symptoms. Urinary urgency remains bothersome, but the estimated improvement has been 80 per cent.

In summary, the Gilliam-Doléris uterine suspension operation may precipitate urinary stress incontinence if technically successful in a patient whose uterus is retroverted as the result of congenital factors. The symptoms are apparently caused by posterosuperior extravesical pressure with diminution and limitation of potential bladder capacity. When these factors are removed, the symptoms of urinary stress incontinence may be relieved.

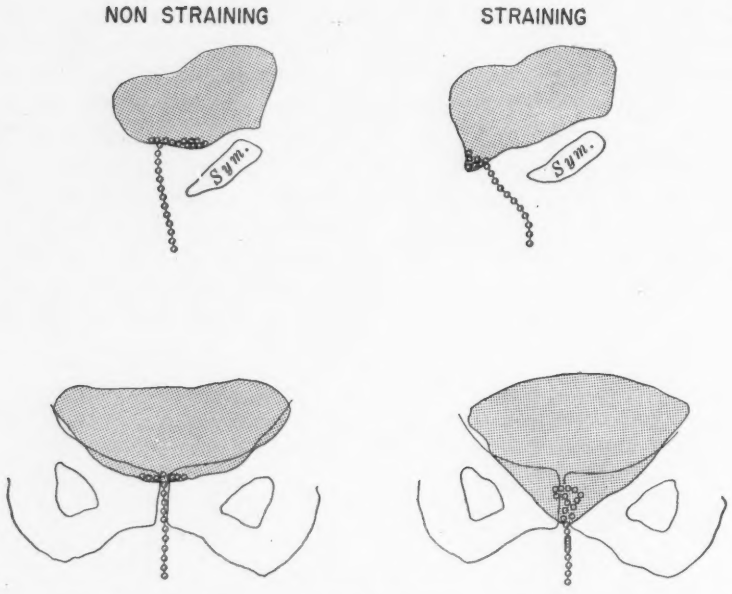

Fig. 17.—Patient 13 (A. G., 633044). Aged 24 years. Urethrocystograms after Gilliam-Doléris uterine suspension.

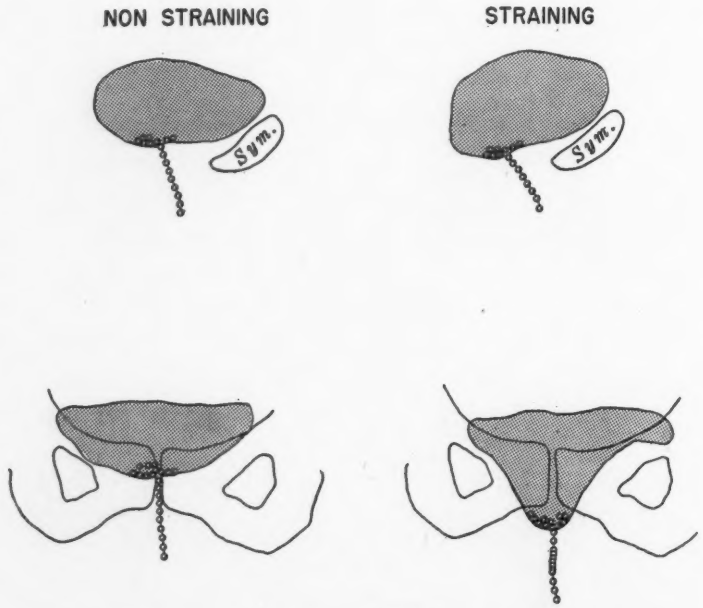

Fig. 18.—Patient 13. Changes effected by vaginal delivery.

Comments

Comparison of urethrocystopubic relationships of five groups of patients disclosed the constraining influences on the bladder base to be of two orders. Support of the first order was afforded by the contiguous structures. In the virginal patient, this support was uniform and continuous. Of the second

order, support could be attributed to the levator ani muscle group. It was incomplete. In the anteroposterior radiograms the space between the two muscles was identified as a potential hiatus.

Parturition effected various deficiencies in first order support. In the normal parous patient of Group 2, the deficiency was minimal. In Group 4, partially defective first-order support allowed vertical descensus of the urethra and bladder. This caused the bladder base to become cone shaped with the internal urinary meatus located at the lowermost bladder level. This anatomical circumstance has been identified with urinary stress incontinence.

A combined deficiency of first- and second-order support was identified in patients included in Group 3. Downward and backward rotation of the entire bladder was usually characteristic of uterovaginal prolapse.

In some patients of Group 3, the bladder prolapse was partial or segmental. This was characterized by a dumbbell-shaped bladder silhouette. The upper bulb of the dumbbell-shaped bladder was supported by efficiently functioning pubococcygeal muscles while the lower bulb had prolapsed through the intermuscular hiatus. This circumstance suggested complete failure of first order support.

Extravesical force and the variable degree of deficiency of urethrovesical support combined to extend the limits of bladder mobility through a vast potential arc. As the result, urethrovesical angles could not be considered static relationships. Their evaluation proved to be inaccurate, and at the best, approximate, because frequently the bladder base and the urethral catenary formed an arc rather than an angle. An effort was made to review under nonstraining and straining conditions, the anterior, lateral, and posterior urethrovesical angles.

Estimation of the anterior urethrovesical angle was subject to the least error. In the normal nonparous patient it was an acute angle and tended to become more acute as she strained. After parturition, in patients with urinary stress incontinence, the "nonstraining" radiograms often revealed the angle to be obtuse and, in many such patients, the anterior and the posterior angles were nearly equal. Upon straining, as the result of vertical, downward displacement of the bladder, the anterior angle was frequently reduced to an acute angle. In patients with uterovaginal prolapse, the anterior angle was usually acute, and straining made it more so.

The lateral urethrovesical angles were symmetrical and usually somewhat obtuse. Their measurement was often impossible because of the end-on position of the metallic beads superimposed over the bladder shadow.

The posterior urethrovesical angle was subject to an unlimited range of variations. In the nullipara the angle was widely obtuse, almost 180 degrees. After parturition, straining effected a variable response: if the bladder rotated anteriorly, the posterior angle tended to become more obtuse; if the bladder plunged downward in a vertical direction, it became a reverse angle; and, in uterovaginal prolapse, the angle tended to become acute because of the downward and backward rotation of the bladder wall.

The admonition to restore the posterior urethrovesical angle as a prerequisite for the surgical cure of urinary stress incontinence is vague and unintelligible when interpreted according to these variable facts.[16–18] It is assumed that restoration of the normal posterior urethrovesical angle connotes the fabrication of an acute, or at least a right, angle. These results suggested that any substantial degree of acuteness of the posterior urethrovesical angle was an artifact of parturition and resulted from downward and backward

rotation of the bladder around a relatively well-fixed urethra. This was the prevailing circumstance in uterovaginal prolapse—a condition usually associated with urinary continence.

Other gynecologists have considered elevation and restoration of the urethrovesical neck to a normal position as essential surgical accomplishments for cure of urinary stress incontinence.[16, 19-21] The radiograms displayed the urethrovesical junction as a "neck" only in patients who complained of urinary stress incontinence. They demonstrated vertical bladder descensus from failure of first-order support. Before parturition, the urethrovesical junction was located posterior to the midcoronal bladder plane. With loss of posterior and inferior support, resulting in backward displacement of the bladder, the relative position of the urethrovesical junction migrated forward to locate at, or anterior to, the midcoronal bladder plane. Operative procedures designed to elevate the urethrovesical junction to a high level immediately posterior to the symphysis pubis located it at a rather unique position for "normal" when evaluated by the standards observed in the present study. These operations produce an acute posterior urethrovesical angle by elevating the urethrovesical junction and causing posterior rotation of the bladder around a well-fixed urethra. The relationships created thereby are those commonly observed in patients who complain of uterovaginal prolapse.

The influence of supravesical pressure in causing urinary stress incontinence was evaluated in 2 patients who had been subjected to uterine suspension by the Gilliam-Doléris technique. Although both complained of embarrassing urinary stress incontinence, neither demonstrated failure of first- or second-order support. Both were relieved of symptoms when the restraining influence of the acutely anteflexed uterus was removed. These observations suggested that urinary stress incontinence might have a varied etiology.

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Discussion

DR. WILLIAM F. MENGERT, Chicago, Ill.—In 1939, Diddle, Mengert, and Earl studied the movement of the uterus with postural change in normal women and in some with prolapse, by means of superimposed photographs and roentgenograms. In a few instances they touched upon delineation of the urinary bladder in women with partial and complete prolapse. With this exception, my knowledge of this subject is limited to reading, and some clinical experience. Therefore, I shall attempt to define stress incontinence and to review briefly its medical and surgical history.

Stress incontinence may be defined as the intermittent, involuntary loss of urine from a system possessing no accessory orifices, of either acquired or congenital origin. It has been only in the past fifty years that serious attention was directed to stress incontinence.

Prior to the twentieth century, incontinence of urine was accorded attention only in the presence of vesicovaginal or ureterovaginal fistula, or of accessory ureters opening below the level of the bladder sphincter. Since vesicovaginal fistula today can generally be cured, attention has gradually turned to women who lose urine from an intact urinary system; in other words, stress incontinence. In recent years we have learned, and Dr. Hodgkinson has reaffirmed, that urinary stress incontinence is associated with definite anatomic change.

An Italian, Giordano, in 1907, made one of the earliest attempts to correct stress incontinence in the female by utilizing a portion of the gracilis muscle to encircle the urethral meatus. In 1910 Goebell devised an operation using pyramidalis muscle. Frangenheim of Cologne performed a similar operation in 1914. So did Stoeckel who published a description in 1917. The operation, therefore, today is called the Goebell-Frangenheim-Stoeckel operation. It was moderately successful and remained essentially unaltered until the time of Aldridge in 1942.

Howard A. Kelly in 1913 published a report of the operation that bears his name. Shortly after Kelly started to work, Baldy also began to develop a similar vaginal plastic operation. However, Kelly antedated Baldy, not only in the time of his work, but also in publication. Kelly's operation is excellent, and we must never forget that the number one operation for stress incontinence of urine today is anterior colporrhaphy, with or without Kelly's modification. This operation will cure 90 to 95 per cent of all women with stress incontinence of urine, and certainly is the desirable *primary* procedure.

After the early work in Germany with musculofascial slings, and in this country with vaginal plastic procedures, practically nothing was written about operative correction of stress incontinence in the female until 1939, with but one exception. This was an article written in 1932 by Norman Miller who revived the Goebell-Frangenheim-Stoeckel operation. His interest started with a preadolescent girl admitted to the University of Iowa Hospitals because of incontinence. A congenital absence of the urethra was corrected elsewhere, but she remained incontinent. It is of great interest that few of the basic principles we know today regarding etiology and treatment of stress incontinence were recognized at the time of Miller's report.

William T. Kennedy, in a series of articles beginning about 1937, pointed out that displacement of the bladder neck from its normal position was basically responsible for stress incontinence.

Berkow approached the matter from a completely different aspect and devised the operation which he called "paraurethral fixation," defining this as an advancement of the urinary meatus and a suburethral reefing of the pubococcygeal portion of the levator muscles, and of the bulbocavernosus.

Very little additional work of significance appeared after Berkow's and Aldridge's contributions until 1949, when Marshall, Marchetti, and Krantz published their classical paper on suspension of the bladder. This operation has proved to be highly satisfactory but, in general, I believe it should not be done until vaginal plastic procedures have been tried, and failed.

It seems to be established beyond a doubt, first, by the work of Kennedy, second, by the work of Marshall, Marchetti, and Krantz, third, by the radiographic demonstrations of Ball, and finally with the demonstrations of the present essayist, that the principal defect, so far as women with stress incontinence of urine are concerned, is a minor degree of sagging of the bladder neck. That is the reason, therefore, that vaginal plastic operation, restoring the bladder neck to its proper anatomic position, is so useful in the correction of stress incontinence. Occasionally, when vaginal plastic operation fails to do this, either the ventral suspension of Marshall, Marchetti, and Krantz or the fascial sling operation devised in Germany, modified by Aldridge, and more recently by Reed, appears to be the procedure of choice.

DR. CURTIS J. LUND, Rochester, N. Y.—The riddle of micturition, whether voluntary or involuntary, continues to challenge gynecologists, urologists, radiologists, anatomists, and physiologists. The mechanics of any complex voluntary and involuntary act are difficult to solve and one might cite for comparison the mechanism of swallowing. The latter problem has at last yielded to x-ray cinefluorography and in our laboratories we are applying this helpful device to a study of urinary function.

The value of serial study cannot be underestimated. The progressive changes in relaxation from age 14 through the menopause are striking. We have observed a 5-year-old girl, as well as a nullipara, exhibit some of the same downward displacement and funnel shape of the urethrovesical junction but only when the patient was coughing.

One of the significant points brought out by the illustrations of this paper concerns the relation of the bladder neck to the most dependent portion of the bladder. In the virgin the most dependent portion was anterior, while in the presence of prolapse there was extreme posterior displacement and neither patient was incontinent.

If the urethrovesical junction is infundibuloform and if this occurs at the most dependent portion of the bladder, then the hydrostatic pressure of exertion is directed upon the most vulnerable area and the patient is likely to be incontinent. If at this time the bladder neck is assimilated into the more anterior portion of the bladder by some type of urethropexy, or by further relaxation of the posterior bladder wall, the patient becomes continent.

The bead technique which Dr. Hodgkinson uses produces excellent posterior-anterior and lateral film with exact location of the urethra and its relation to the bladder. One of the chief disadvantages of this static technique is the lack of motion. Fluoroscopy, by contrast, reveals a series of complex movements when the patient coughs, strains, or voids which can be readily missed with a single x-ray film as some are of no longer duration than 0.1 to 0.2 second.

Might not the "anterior rotation" of the bladder seen in young girls and the "posterior rotation" observed in older parous women be explained by the position of the uterus? Have you attempted to correlate uterine position with the rotation of the bladder?

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—At the Hospital of the University of Pennsylvania a program is under way in the effort to determine the relationship of the urethra to the bladder by means of roentgen anatomy. During the past three years 180 lateral cystourethrograms, as suggested by Hodgkinson and by Jeffcoate, have been made—with modifications of the urethral contrast medium. In this study we are attempting to evaluate three things: First is the relationship between the bladder symptoms and the radiographic findings. Thus far, no constant radiographic alteration has appeared to explain all instances of true stress incontinence, but the lack of any radiographic change from the normal has interdicted attempts at surgical intervention. Second, comparison of the radiographic appearance both before and after corrective surgery, with attempts to correlate the new anatomic picture and the functional result, in the effort to determine the factors which contribute to success or failure. Third, the possibility that, as this study

progresses, we will be able to determine from the first picture not only whether operation can be expected to be successful but also the type of surgical procedure that has the greatest chance of success in the face of a given problem.

It is our hope that such a program—namely, radiographic study of the bladder and urethra, after as well as before operation, with the effort to correlate the functional and the anatomic results with the type of surgical procedure that has been done—may give us a lead as to whom to operate upon and what type of surgical procedure to use for a given problem.

DR. HODGKINSON (Closing).—Dr. Mengert's comments on the history of the surgical procedures recommended for the correction of urinary stress incontinence were most interesting. This paper was intended, however, to demonstrate the alteration in urethrovesical relationships in the conditions mentioned and pertained to the problem of urinary stress incontinence only indirectly.

I agree with Dr. Lund that a major defect of this method of investigation is that it fails to demonstrate motion. We see the result of motion, but not the motion per se. I hope to have the opportunity of reviewing Dr. Lund's cinematic studies, as I am sure his results will add a great deal to our knowledge of bladder physiology.

In reply to Dr. Lund's question whether anterior or posterior rotation of the bladder depends to any extent upon the position of the uterus, I can state that in my opinion the answer is "yes." I am also quite sure that evidence strongly suggests that the position of the uterine fundus depends upon its relationship to the bladder. The patient with a congenital retroversion of the uterus whose cervix is located far forward on the anterior vaginal wall is likely to have the uterine fundus displaced posteriorly when the bladder fills with urine. Patients with that anatomical circumstance frequently have a propensity for vertical descensus of the bladder without rotation. This important anatomical relationship should be investigated further.

TUMORS OF THE BROAD LIGAMENT* †

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THIS is our seventh publication on various aspects of data accumulated from studies of broad ligaments. Previous reports have recorded portions of those data as they relate to normal and cystic structures of the broad ligament,[1] metaplasia of tubal epithelium,[2] preinvasive carcinoma of the uterine tube,[4] peritoneal bodies and cysts of the broad ligament[6] (so-called "Walthard bodies"), the diverse origins of Brenner tumors,[3] and so-called carcinogenic cells[5] (interstitial or hilar cells). The foregoing seems to be a weird conglomeration of unrelated topics, but most of the material for these publications actually had a common source of origin; it was derived from a collection and study of microscopic preparations of broad ligaments.

Originally, these studies were undertaken in an endeavor to overcome a long-standing state of frustration over the then current methods of classifying broad ligament cysts, and, to quote the introduction in our first paper:

"The literature on broad ligament cysts was reviewed in an attempt to find or to formulate an accurate classification of these structures. The results were unexpectedly confusing. The terminology used by various authors was highly individualistic. The following names were noted: paratubal cyst, parovarian (also para-ovarian, parovarial) cyst, Wolffian cyst, intraligamentous cyst, Kobelt's cyst, epoophoral cyst, fimbrial cyst, junctional cyst. The remnants of the embryonic mesonephros (Wolffian body) from which most authors believe these cysts to be derived, were called variously: Wolffian body, epoophoron, Organ of Rosenmüller, Kobelt's tubules, parovarium, parovarial tubules. Anatomical descriptions, particularly as to histology, were equally varied. Opinions on histogenesis were less diverse, but were frequently beclouded by two factors: (1) There seems to be little specific knowledge of the structures that are present in the normal broad ligament. (2) Of even greater importance were the contradictory and frequently inadequate or even erroneous concepts of the embryonic development of broad ligament structures. One of the erroneous concepts was traced to the assumption that details in the embryonic development of the rete in the tortoise were directly applicable to man.

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"The terminologic welter, histologic melange, and embryologic diversities left us in a state of mind that could best be described as one of 'chaotic confusion.' It was, therefore, decided to study the embryonic development of broad ligament structures, then the normal adult broad ligament, both in routine and in serial section, and, finally, the abnormal broad ligament."

I. The Normal Adult Broad Ligament

A. Mesonephric (Wolffian) and Paramesonephric (Müllerian) Structures.—

Serially sectioned specimens from 14 embryos and newborn infants were studied; so too were routine blocks of broad ligaments, tubes, and ovaries from 598 patients; some of these were normal tissues and others were pathologic. We also studied serial sections from the lateral half of 11 broad ligaments from adult women.

Studies of tissues from embryos confirmed certain fundamental observations by others: first, that the mesonephric duct and some 80 mesonephric tubules are originally a part of the mesonephros (or Wolffian body); and, second, with formation of the definitive kidney, the mesonephros almost completely disappears. However, at least the caudal one third of the mesonephric duct and some 10 to 15 mesonephric tubules connected with the cranial part of the duct remnant in the embryo are consistently preserved and persist as such throughout adult life, and are composed of fully differentiated, adult-type tissues. In the Cohnheim sense they are not "embryonic rests." Since these are the same structures that are found in the embryo, we shall refer to them only as mesonephric duct and mesonephric tubules; we see no reason to call them by any other of the names with which they have been saddled.

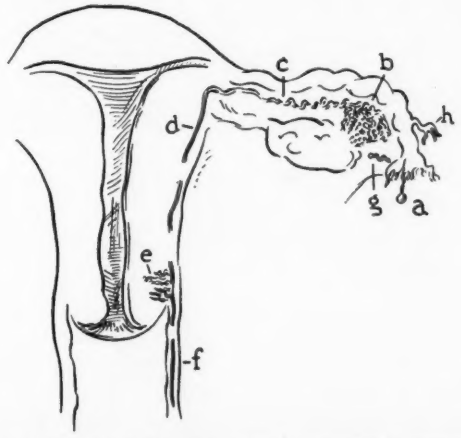

Fig. 1.—A diagram of mesonephric and paramesonephric structures that may be found in the normal adult female: *A*, pedunculated paramesonephric "cyst" (hydatid of Morgagni); *B*, mesonephric tubules connecting with the mesonephric duct; *C*, mesonephric duct that may be present in the more mesial portions of the broad ligament; *D*, in parametrium or lateral aspect of the uterus; *E*, ramifications that may be found in the cervix; *F*, in the lateral vaginal wall; G, paramesonephric tubule that may be found in the broad ligament; *H*, accessory oviduct. (From Brewer, John I.: Textbook of Gynecology, Williams & Wilkins, 1953; lent to Dr. Brewer by Dr. Gardner.)

In addition we encountered occasional tubules in and on adult broad ligaments which undoubtedly are paramesonephric (or Müllerian) derivatives; some of these actually are accessory or miniature tubes, and may be attached to the broad ligament anywhere; they probably result from a developmental defect in the formation of isolated fimbriae. Actually such defects are almost inherent in paramesonephric derivatives, since, as their name implies, they are

absolutely dependent on close proximity to and guidance by the mesonephric duct for an orderly progressive growth, for differentiation, and for proper development.[1] The 10 to 15 mesonephric tubules which persist into adult life are not evenly spaced throughout the broad ligament, at least not in the manner which has been depicted for years in usual textbook illustrations. Actually, they are closely grouped (Fig. 1) in the most lateral one third of the mesovarium where one end of a mesonephric tubule is in close juxtaposition to the rete ovarii and frequently communicates with it. Thence they extend upward through the most lateral mesosalpingial portions of the broad ligament to the mesonephric duct. (The precise location of these structures becomes readily apparent when one views a fresh broad ligament against a bright light.)

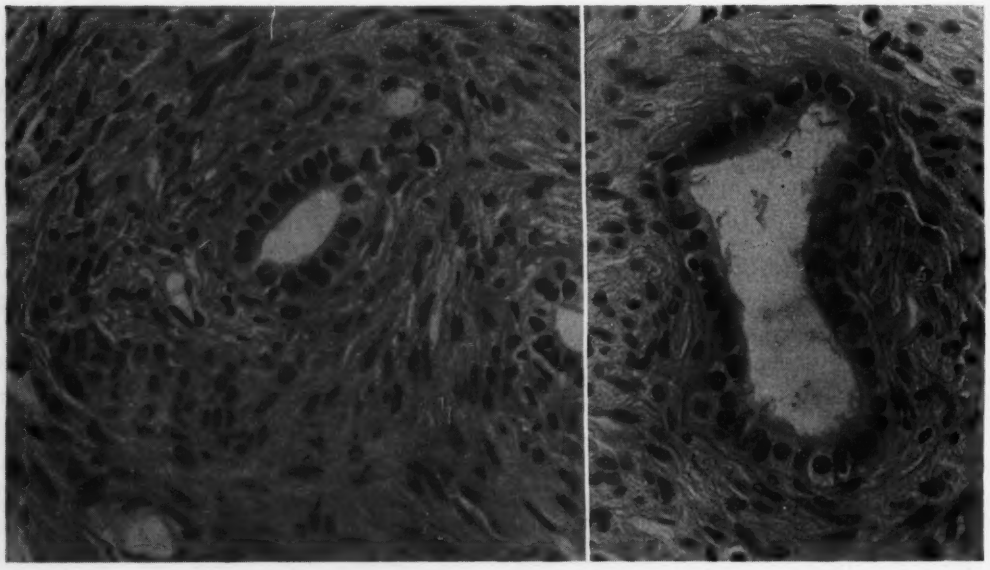

Fig. 2. Fig. 3.

Fig. 2.—A cross section of mesonephric duct as found in the broad ligament. Note the simple cuboidal epithelium. (From Gardner, Greene, and Peckham.[1])

Fig. 3.—A cross section of a mesonephric tubule. Ciliated and "secretory" cells are present. (From Gardner, Greene, and Peckham.[1])

It soon became obvious to us that these studies would be greatly facilitated if routine blocks were so cut that one section would include the base of the ovary and the mesosalpingial portion of the tube, as well as the broad ligament. (Of course such sections are not found in laboratories where tubes are dissected from ovaries before blocks are taken from each of them, separately.) Soon we also recognized that only those microscopic preparations of best quality were of definite value, since certain details in the accurate differentiation and identification of various normal structures, as well as abnormalities in them, were largely dependent on the finer histologic characteristics of these particular broad ligament tissues. Autolysis and dessication result from the usual delay in placing operative specimens in proper fixatives. Harsh fixatives give rise to undue shrinkage and distortion of cell structures. Rushing tissues through an Autotechnicon and other mass-production methods resulting from the demands on technicians in most present-day laboratories cause further damage.

The foregoing all-important technical details, i. e., the preferred site and extent of blocks, prompt and careful fixation of tissues, and high quality of

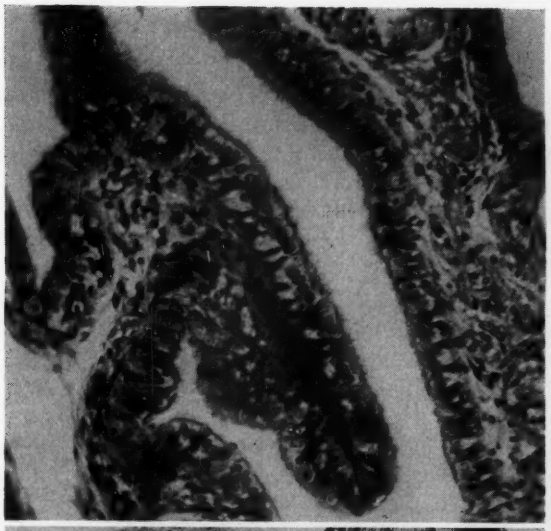

Fig. 4.

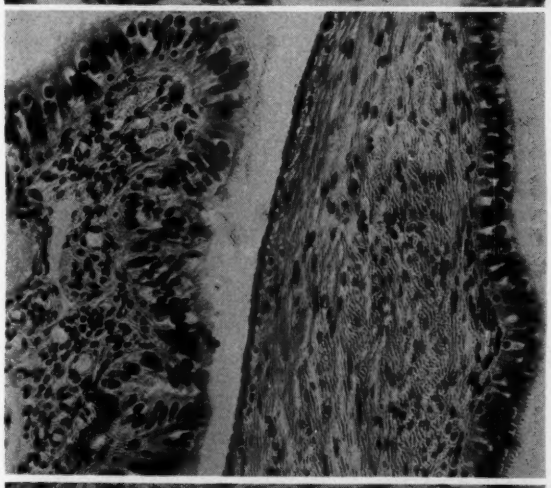

Fig. 5.

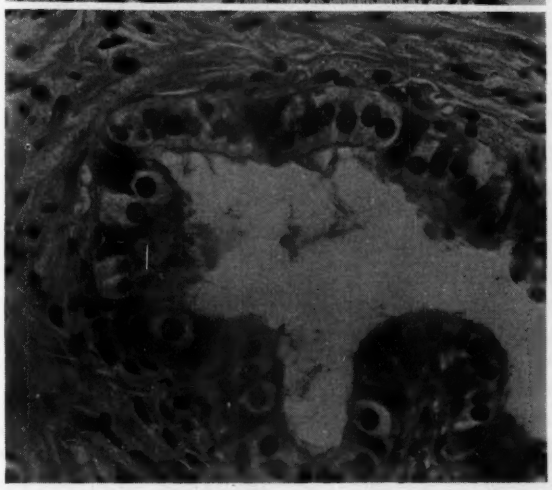

Fig. 6.

Fig. 4.—Normal oviduct epithelium in estrogenic phase. (From Gardner, Greene, and Peckham.[1])

Fig. 5.—On the left is oviduct fimbrial epithelium in the progestational phase. Note the projecting nuclei of secretory cells. The low cuboidal epithelium in the middle is peritoneal mesothelium. The epithelium on the right is that of a paramesonephric cyst and is similar to that of the oviduct.

Fig. 6.—A paramesonephric tubule found in the broad ligament. The cells are larger than in mesonephric tubules and show hormonal changes. This specimen shows progestational changes and is identical to the oviduct epithelium. (From Gardner, Greene, and Peckham.[1])

microscopic preparations, must be reiterated because they are essential in studies of this type. Lack of attention to such details in technique, more than any other single factor, was responsible in all probability for the confused previous state of knowledge about normal structures in adult broad ligaments. Also, a failure to abide by these specifications may prevent future workers in this field from confirming certain of our observations. Those which are fundamental, include the following:

(a) The *mesonephric duct* (homologous to the body of the epididymis and the vas deferens in the male) is found close to but outside the musculature of the tube and is probably always present in the lateral half of the broad ligament. Usually its course is gently undulating. Portions of the duct may persist in the mesial part of the broad ligament and continue downward in the parametrium beside the corpus, to and into the lateral portions of the stroma of the cervix, and then along the lateral wall of the vagina. This duct has its own discrete musculature, which includes inner longitudinal and outer circular fibers, similar to the ureter. It is lined by a single layer of low cuboidal epithelial cells (Fig. 2) with mesially placed nuclei (at least in its broad ligament, parametrial, and cervical portions).

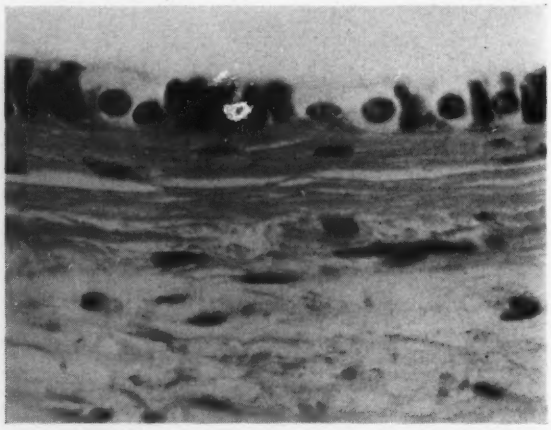

Fig. 7.—The wall of an intraligamentary cyst of mesonephric tubule origin. Note the similarity of this epithelium to that of Fig. 3. (From Gardner, Greene, and Peckham.[1])

(b) *Mesonephric tubules* (homologous to the efferent tubules and conus epididymis of the male) are more highly convoluted; they extend from the rete ovarii to the mesonephric duct. Their musculature is similar to but less well developed than that of the mesonephric duct; in fact, as mesonephric tubules near the rete, this muscular coat is lost. On the other hand, the epithelium lining these tubules is more specialized than that in the duct; the cells are low columnar, and of two types (Fig. 3), i. e., ciliated and nonciliated, or secretory. The cytoplasm of ciliated cells stains lightly; nuclei are large and centrally located; cilia are prominent. In contrast, the cytoplasm of secretory cells stains more darkly; the cells are more narrow, and may even appear compressed.

(c) *Paramesonephric derivatives* (including uterine tube and structures found in and on the broad ligament) are lined by an epithelium similar to but not identical with that of mesonephric tubules. It, too, consists of both ciliated and secretory cells. Such epithelium varies in appearance during different phases of the menstrual cycle. It is high, and all cells are high columnar and of the same height, in the estrogenic phase (Fig. 4); whereas in the progestational phase, the secretory cells are relatively higher than

ciliated cells (Fig. 5) and their nuclei may even project into the lumen of the tube. Occasionally one finds tubules in broad ligaments (Fig. 6) whose epithelium is identical with that of uterine tubes, both in histologic appearance and in its response to hormones. Also to be classified in this category are so-called accessory oviducts or accessory tubes; these are tiny inconspicuous

Fig. 8.

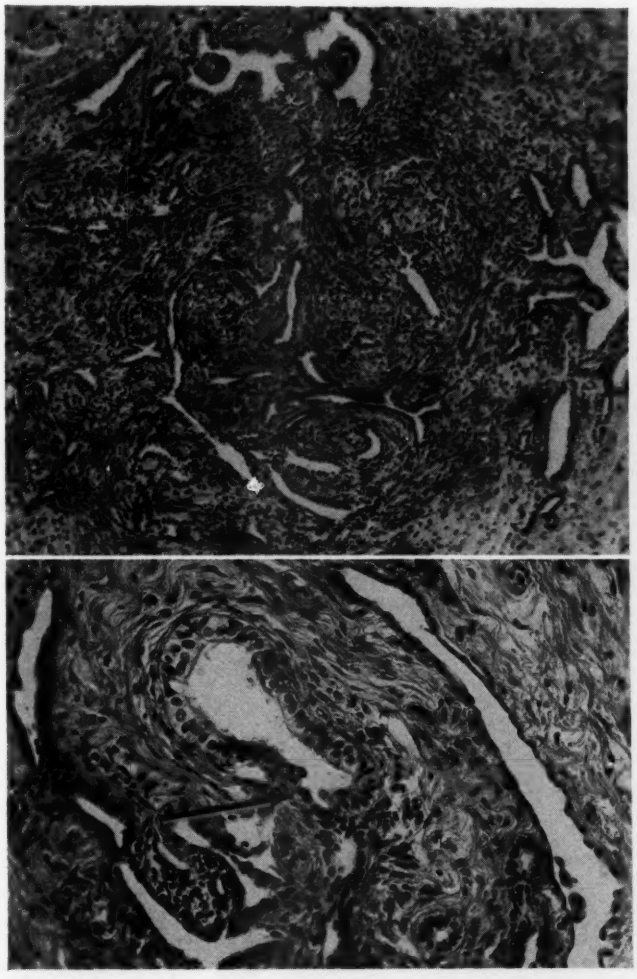

Fig. 9.

Fig. 8.—A normal rete ovarii. Note how well developed and complex is this structure.

Fig. 9.—Shows a communication of mesonephric tubule with rete. The arrow points to junction of typical mesonephric tubule epithelium with low cuboidal epithelium of the rete.

structures of variable length and width, projecting out from the broad ligament and possessed of open fimbriae. Certainly they are far too common to be considered pathologic, although it is readily admitted that the frequency with which they are found depends chiefly on one's industry in looking for them. Accessory oviducts are truly miniature uterine tubes, with the usual plica or folds, and with identical epithelium that undergoes the same hormonal responses and with a lumen that is usually short; although we have one specimen in which the lumen penetrates deeply into the broad ligament.

There are several distinct differences between mesonephric tubule and paramesonephric structures, although their lining epithelium bears a considerable resemblance and in a few respects that of mesonephric tubules is simply a junior edition of that which lines the oviduct. Here are some of the distinct differences: Paramesonephric epithelial cells are 50 per cent larger, and so too are their nuclei.[1] Mesonephric epithelium (both duct and tubule) has a well-defined basement membrane, and this is distinctive of it. Paramesonephric derivatives are characterized by so-called "villi"; actually these are nothing more than cross-sectioned transverse folds or plica; they are not villi. Also, the epithelium of the mesonephric tubule does not show the characteristic hormonal changes found in the oviduct, either of the progestational phase of the cycle, or menses, or of pregnancy.

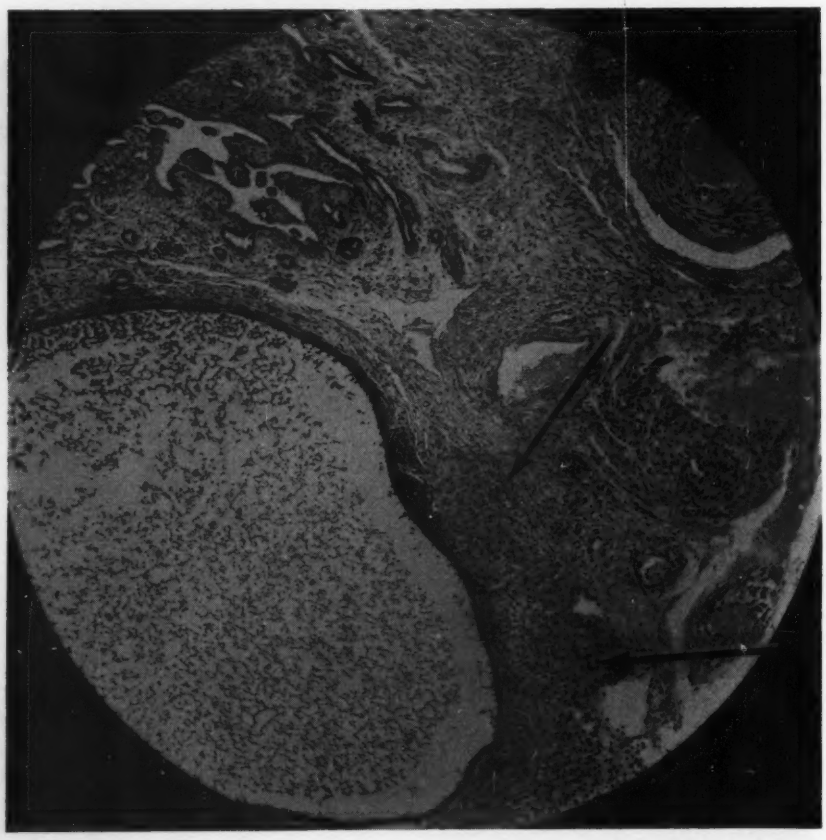

Fig. 10.—Shows normal rete above and an area of cystically dilated rete below. Immediately to the right of this latter structure there is an accumulation of hilar cells (arrows).

Hence, in the identification of various epithelium-lined structures in the broad ligament, whether normal, cystic, or tumorous, it is extremely helpful, in fact practically essential, that a cross-section of uterine tube be included, for comparison of its epithelium with that lining the structures under scrutiny.

We next studied 101 broad ligament cysts, pedunculated and intraligamentary. Their walls were quite thin and composed of connective tissue and muscle fibers. Such cysts are not neoplasms; they are only distention phenomena and nothing more. We attempted to determine in each one, on the basis of the lining epithelium, whether it was of mesonephric or paramesonephric derivation. This was possible in 87, or 86 per cent of the series.

Twenty-four pedunculated cysts (so-called "hydatids of Morgagni") were suitable for study; 22 (90 per cent) were of paramesonephric origin (actually these are hydropic accessory tubes) (Fig. 5); one, of mesonephric tubule origin; and one, of mesonephric duct origin. Of those which were intraligamentary, whose origin could be identified, 10 per cent arose from mesonephric duct; 50 per cent, from mesonephric tubule (Fig. 7); and 40 per cent, from paramesonephric derivatives.

Fig. 11.

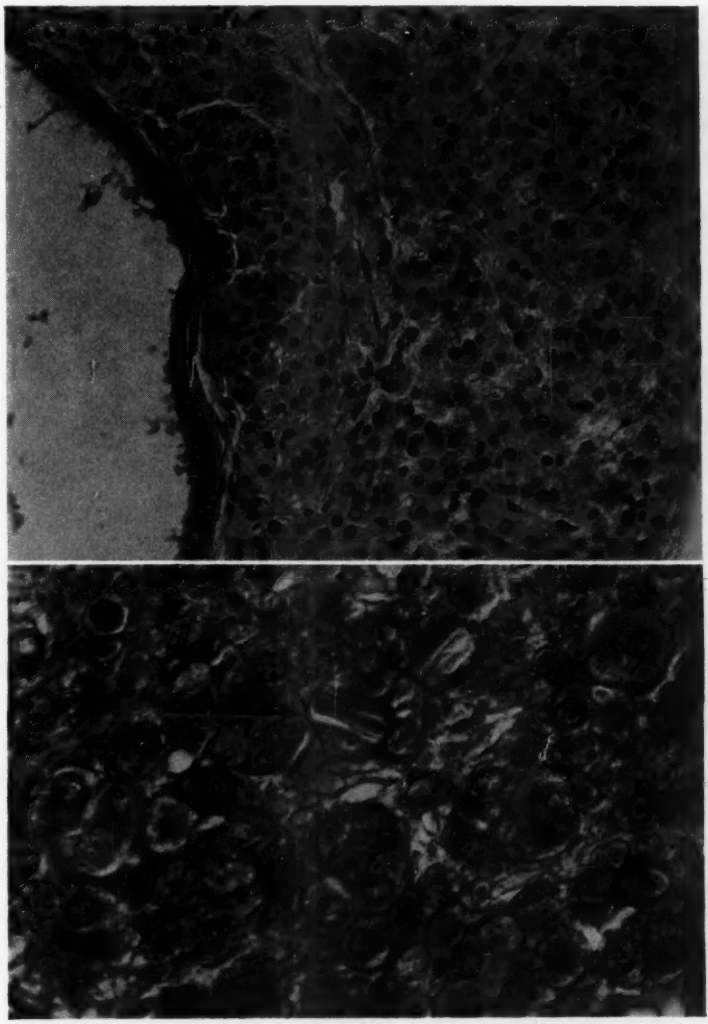

Fig. 12.

Fig. 11.—A high-power photomicrograph showing cystic rete to the left and hilar cells to the right.

Fig. 12.—A still higher power of a section from the same block stained by the Milligan trichrome method. The arrow points to a typical oblong crystalloid of Reinke.

As a result of these studies we concluded:

1. Much of the existing confusion in classifying normal and cystic structures of the broad ligament can be eliminated by discarding terms based on proper names, and by using only those which have histogenic significance.

2. Certain well-developed and adult-type structures derived from the embryonic mesonephros are present in adult broad ligaments and can be demonstrated quite readily in properly fixed, properly sectioned, and properly prepared tissues.

Embryologists have appropriately termed them in embryos as mesonephric duct, mesonephric tubule, and paramesonephric structures; hence it is both logical and desirable that they be accorded the very same terminology when they persist as such through adult life, rather than to be labeled with thoroughly confusing names, such as Wolffian duct or longitudinal tubule of epoophoron; Wolffian tubules, Kobelt's tubules, epoophoral tubules, or transverse tubules of epoophoron; and Müllerian duct, respectively.

3. Mesonephric duct, mesonephric tubule, and paramesonephric structures, as well as their respective cystic derivatives, have an individual and characteristic histologic appearance; each can be identified in properly fixed and properly prepared sections on the basis of the character of their lining epithelium.

4. It is impossible to classify them accurately on the basis of their location in the ligament.

Fig. 13.—Bilateral broad ligament cystadenomas. Note that they are completely separate and distinct from the ovaries. (From Brewer, John I.: Textbook of Gynecology, Williams & Wilkins, 1953; lent to Dr. Brewer by Dr. Gardner.)

Such broad ligament retention cysts should properly be termed either pedunculated or intraligamentary depending on their relationship to the broad ligament, and as of mesonephric duct, mesonephric tubule, or paramesonephric origin, depending on the character of their lining epithelium. How much more simple and logical is such a classification, and how futile to perpetuate the archaic "Kobelt cyst, hydatid of Morgagni, and appendix vesiculosa; or epoophoral, fimbrial, intraligamentary, intraligamentous, junctional, para-ovarian, parovarial, parovarian, paraovarium, paratubal, and Wolffian cyst!"

B. Other Structures Found in the Normal Broad Ligament.—

Rete ovarii. Due to the precise site from which preferred blocks are cut, the hilum of the ovary is included in our sections. We have found that the rete ovarii is present in all normal adult females and is a well-developed structure. In fact it is almost comparable in size to that of the male, and not as it is usually dismissed in textbooks an atrophic remnant, merely a shrivelled edition of its brother, the rete testis. Admittedly, the rete is less conspicuous in

hematoxylin-eosin sections than in those stained by the trichrome technique, and it is also true that the female rete does not have the functional significance of the rete testis. Yet it appears surprisingly healthy and well preserved in properly fixed and properly stained specimens. It is composed of a complex network of epithelium-lined irregular spaces, epithelial cords, and epithelial

Fig. 14.

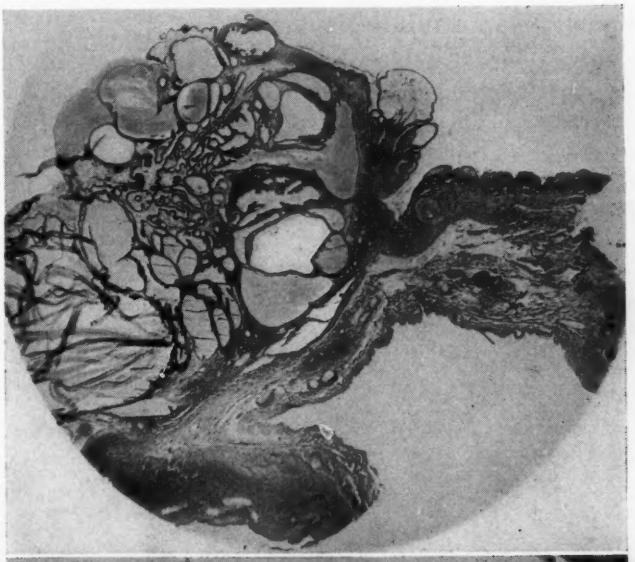

Fig. 15.

Fig. 14.—A low-power photomicrograph from the right-sided intraligamentous tumor of Fig. 13. The luminal surface is at the top. Note the papillary ingrowths.

Fig. 15.—A high-power photomicrograph from the same area as Fig. 14. The epithelium is a simple, high columnar type.

tubules (Fig. 8). If one looks for them, he will frequently find sites of junction of mesonephric tubules with rete ovarii (Fig. 9), although these are said not to occur in females. The epithelium of the irregular clefts and more central tubules and cords is low columnar and there is no basement membrane. On the

periphery, the epithelium may be columnar with nuclei that are creased or infolded[3]; also in that location there is a basement membrane. In reality this change in the epithelium at the periphery represents the junction of the rete with medullary tubules or cords.

Although the rete, strictly speaking, is not a broad ligament structure, rete cysts project into and cause enlargement of the broad ligaments. Such cysts also are distention phenomena, not true tumors. This subject will be discussed in some detail in a future publication.

Medullary tubules are homologous to the tubuli recti of the male. They are not common but when present may extend from the rete to and into the medulla of the ovary. This subject will also be discussed in future publications.

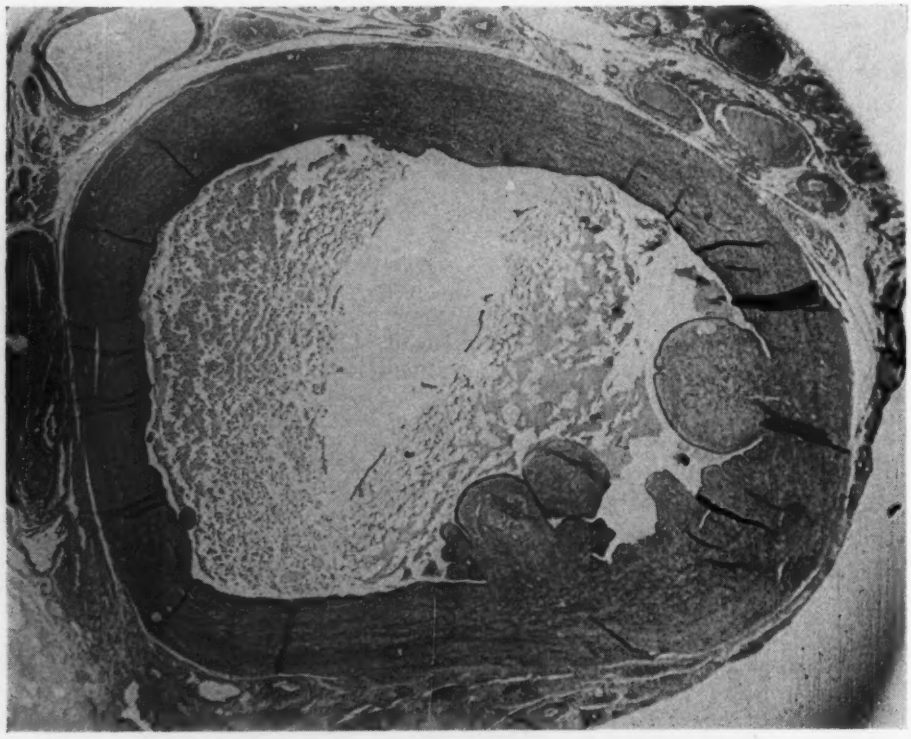

Fig. 164.—Low power of a thick-walled, fibropapillary cystadenoma of the broad ligament.

Hilar or interstitial cells are constant findings in normal adult female broad ligaments (Fig. 10). This subject was discussed in a previous publication[5] and the references will not be repeated here. Such cells have a distinct cell membrane, uniformly shaped nuclei, and a considerable amount of eosinophilic staining cytoplasm in which, with proper staining, crystalloids of Reinke can sometimes be demonstrated (Figs. 11 and 12). As one should anticipate, there is great variation in the number of interstitial cells found in different individuals, but apparently they are both a universal and a normal finding; probably they produce at least a portion of the androgen elaborated in every female.

Accessory adrenals are fairly common findings in normal broad ligaments. With the exception of an absence of a medulla they are counterparts of normal human adrenal glands, including a characteristic capsule, appearance of

individual cells, arrangement of cells in relation to each other, and in the lack of connective tissue containing collagen within the substance of the gland.

II. Tumors of the Broad Ligament

Definition.—Tumors of the broad ligament may be defined on the basis of *location* as those which occur *in* or *on* the broad ligament, but are completely separated from and are in no way connected with either the uterus or the ovary. In this study, the hilar region of the ovary and the mesovarium are considered to be a part of the broad ligament. Hence tumors of the rete ovarii will be included here.

The usual mesonephric and paramesonephric cysts of broad ligaments are not true tumors; they are merely distention phenomena. Their walls are composed of compressed connective tissue and muscle fibers but they are relatively thin, in contrast to true cystic neoplasms in which the fibrous tissue wall of the cyst takes an active part in the growth. Further, in distention cysts of paramesonephric origin, usually one may find attenuated or stubby so-called "villi" which in reality are only cross-sections of plica or mucosal folds, just like those in the uterine tube. These have been erroneously interpreted by some as "papillae"[1] and the cyst as a neoplasm, particularly in poorly fixed and poorly prepared sections.

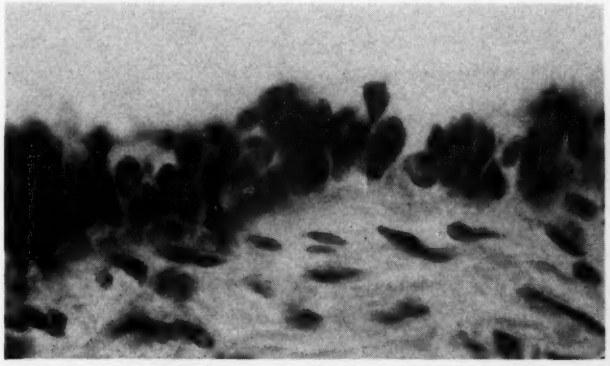

Fig. 16*B*.—High power of an area from Fig. 16*A*. The lightly staining cells are ciliated.

In respect to size, most of the tumors which we shall describe were small; in fact many of them were only chance findings in microscopic preparations. In respect to symptoms and clinical significance, most of these tumors were of only academic importance and were found because our group is interested in and looks for abnormalities in broad ligaments. In the few instances where these tumors actually had clinical significance, the history and clinical problem will be related for those individual specimens.

Our series includes 27 tumors of the broad ligament. These have been divided into the following categories:

Myoma	3
Fibroadenoma (pedunculated)	1
Cystoma, serous	5
Cystadenoma, serous	9
Brenner tumor	5
Granulosa-theca cell tumor	1
Adenoma, rete	1
Adenoma, paramesonephric	1
Adenocarcinoma	1
Total	27

One small mucinous cystadenoma, or more properly mucinous cystadenofibroma, was not included because it probably arose in the medullary region of the ovary and not the hilum or mesovarium.

Three Myomas.—It was deemed necessary to omit from this study all myomas in which there was the slightest question either of extension from or connection with the uterus. That restriction promptly excluded all of the larger myomas; hence these three are tiny tumors. One was located on the tube and apparently arose from its musculature. The others were minute and were deep in the broad ligament, actually located near the rete in the hilum of the ovary.

Five Serous Cystomas.—Tumors of this type must be differentiated from distention cysts. This is accomplished primarily by the collagen fiber character and especially the thickness of the fibrous tissue wall. Both true cystomas and distention cysts may be lined by a simple type of epithelium, either cuboidal or low columnar and by either a uniform type of cells or a "two-cell type" of epithelium.

Fig. 17.—Low power of a granulosa-theca-cell tumor of the broad ligament. The ovary is to the left and the tumor to the right with the cross-sectioned oviduct in the upper right.

One of these cystomas had clinical significance. It was 12 cm. in diameter and was removed by Dr. Greene during the fourth month of pregnancy. He had watched it for six weeks; clinically he considered it to be an ovarian tumor, so waited until he believed the implantation of the pregnancy stable; of course he was able to enucleate it from the broad ligament without disturbing either the tube, or the ovary, or the pregnancy. The patient made an uneventful convalescence and was delivered at term.

Nine Serous Cystadenomas.—These tumors varied greatly in size; some were tiny. All had thick walls; some were simple and others were papillary. Fig. 13 is a photograph of the gross specimen of bilateral serous cystadenomas; each of them is separate and distinct from its corresponding ovary. Also the tubes bend over each tumor similarly. This specimen was obtained from a postclimacteric woman who complained of right lower quadrant pain of recent duration. Her complete general workup was entirely negative. The

right adnexal tumor was recognized and because of tenderness and lack of mobility was considered by Dr. Gardner to be an ovarian malignancy; hence operation was urgently recommended. These tumors were papillary cystadenomas. Fig. 15 is a high-power photomicrograph of the epithelium; cilia were not present. Three years have passed and the patient is free from symptoms and apparently well. Fig. 16*A* is a low- and Fig. 16*B* is a high-power photomicrograph from a smaller papillary cystadenoma of the broad ligament noted grossly at operation by one of us (G. H. G.). It showed a more typical two-cell type epithelium.

Fig. 18.

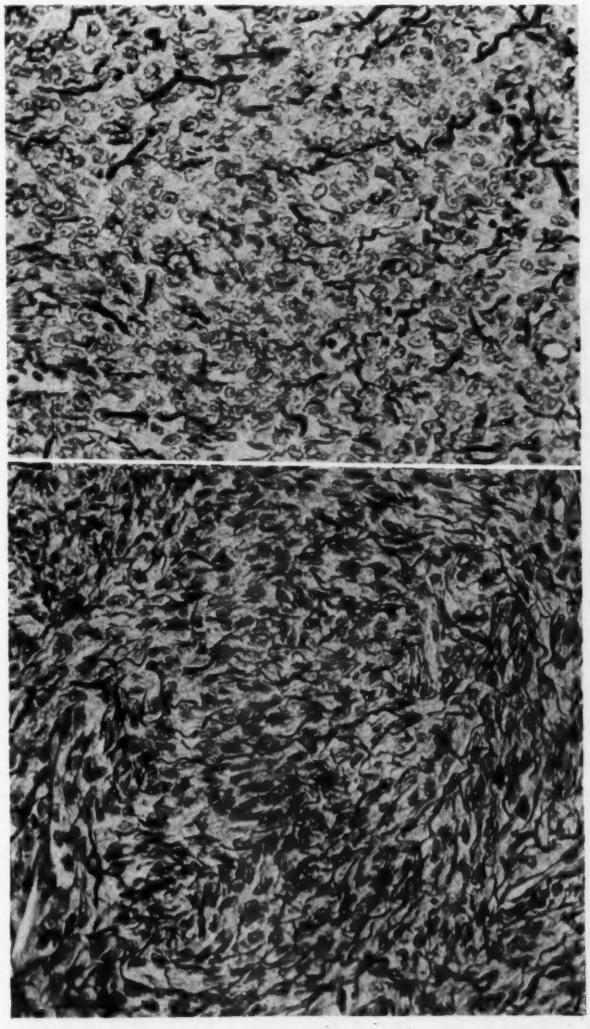

Fig. 19.

Fig. 18.—A granulosa-cell area. This is a Wilder reticulum (counterstained with hematoxylin and eosin) preparation. Note that the black reticular fibers are around groups of cells.

Fig. 19.—A similar preparation from a theca-cell area. Note that the reticular fibers tend to surround individual cells.

Five Brenner Tumors.—One of us (Dr. Greene,[3]) has written in detail about "The Diverse Origins of Brenner Tumors" and therein has recorded that some (but not all) Brenner tumors originate from the rete. Usually they

are tiny and chance findings. Five such tumors are included here as tumors of the broad ligament; all were actually located in the hilum and/or medulla of the ovary. Additional specimens were noted of metaplasia of rete epithelium into typical "Brenner" epithelium but they were not considered to be tumors, because of the paucity of fibrous stroma. In most of those that were catalogued as true Brenner tumors of rete origin, there was continuity with the normal rete or mesonephric tubules.

One Granulosa-Theca-Cell Tumor.—This specimen was obtained at laparotomy in 1948 by Dr. Greene from a 64-year-old woman. Her menopause occurred at the age of 40, i.e., in 1924; at 58, in 1942, she had had a curettage because of uterine bleeding and had been told that the curettings showed hyperplasia of the endometrium. Two years later the bleeding recurred; she was again curetted; again the diagnosis was hyperplasia and she was then given 2,400 mg. hr. of intrauterine radium. Four years later she came to Dr. Greene; as was to be expected he found an extensive adenocarcinoma of the endometrium which also involved the upper portion of the endocervix. In addition, there was a 3.5 cm. solid tumor of the right broad ligament (Fig. 17), completely separate both from the tube and from the ovary. In part, this tumor shows a typical granulosa-cell (Fig. 18) component, and in part it is composed chiefly of theca cells (Fig. 19), with areas of transition between the two.

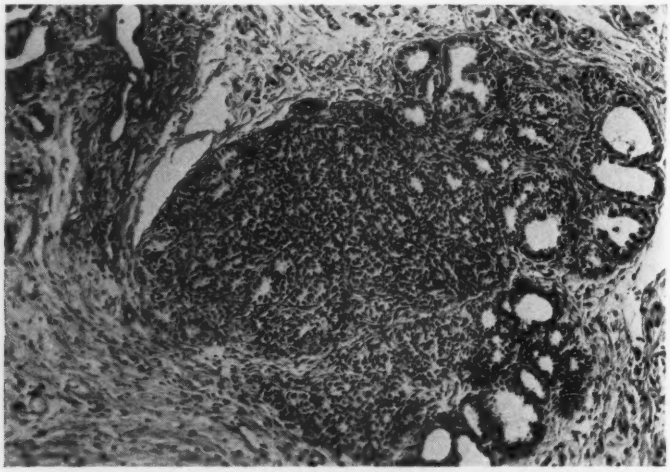

Fig. 20.—A rete adenoma of the broad ligament. There was continuity between this tumor and the adjacent normal rete in the serial sections. In this photograph, part of the normal rete is to the top, left.

This patient survived for three years and presumably died of a cerebrovascular accident. An autopsy was not performed, however, so we are not certain about the exact cause of death and we do not know about recurrence of the cancer.

Incidentally the cross-files in our laboratory of the Department of Obstetrics and Gynecology at Northwestern University include a total of 55 granulosa-theca and theca-cell tumors derived from the several Medical School affiliated hospitals. This particular case is one of the two in that group which is associated with carcinoma of the endometrium. It should be added that, in our opinion, such association in this patient was merely fortuitous and accidental, and in no way bespeaks a cause-and-effect relationship.

One Rete Adenoma.—This tumor was a chance finding in serial sections of the lateral half of a broad ligament. In those serials, the epithelium of the

tumor is continuous with that of the normal adjacent rete ovarii. The tumor is composed (Fig. 20) of interconnecting tubules and cords and is similar in appearance to one reported by Robert Meyer[7] which he considered to be a well-differentiated arrhenoblastoma.

Fig. 21.

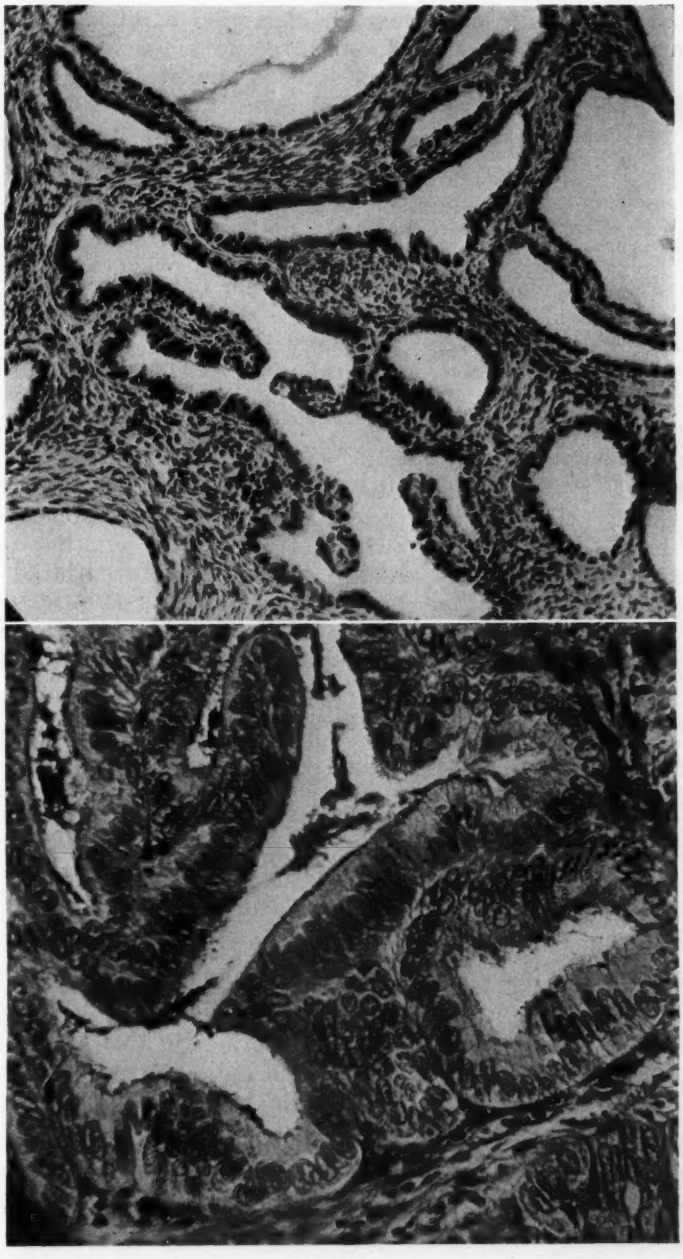

Fig. 22.

Fig. 21.—Paramesonephric adenoma of the broad ligament. The epithelium of this tumor was identical with that of the oviduct.

Fig. 22.—High power of the adenocarcinoma of the broad ligament.

The patient from whom our tumor was obtained did not show evidence of masculinization; this should not be surprising since there were no interstitial cells associated with the tumor and very few were found in the broad ligament.

One Paramesonephric Adenoma.—This was a small swelling in the broad ligament extending downward into the hilar region of the ovary. Sections of it show a very definite fibrous stroma background as one would expect in a true tumor, and epithelial elements consisting of both ciliated and secretory cells (Fig. 21). The epithelium of the tumor is identical with that in the nearby uterine tube, i.e., the same size cells showing the same hormonal response. Hence there can be little doubt that this particular adenoma is of paramesonephric origin.

One Adenocarcinoma.—This material was obtained from Dr. John I. Brewer, although two of us (R. R. G. and G. H. G.) had seen the patient prior to operation. Her complaints were limited to pain and weakness of the left leg. She was approximately 50 (but reluctant to give her exact age), and a nullipara, with a hard left lateral fixed pelvic tumor that was separate from the uterus and extended downward into the paravaginal tissues. X-ray studies showed displacement without involvement of the left ureter; an "erosion" of the left ilium; and at least one distant metastasis, in a rib. Hence, preoperatively this was thought to be a malignancy of extragenital origin. At exploratory laparotomy Dr. Brewer found that the tumor was in the left broad ligament and inoperable; it did not involve either the tube, ovary, or uterus.

Microscopically, the biopsy of the tumor showed well-differentiated adenocarcinoma (Fig. 22), presumably arising from one or another of the broad ligament structures. Strangely enough, this well-differentiated adenocarcinoma showed a beautiful (albeit temporary) clinical response to deep x-ray therapy. The tumor in the rib disappeared and for a while the tumor in the pelvis involuted markedly. The patient lived for twenty-seven months after the operation.

Comments

We are fortunate in that all of the gynecologic operative specimens from both Chicago Wesley Memorial Hospital and Passavant Memorial Hospital reach our laboratory at Northwestern, after the hospital pathologists have cut their blocks and made their official reports. (Parenthetically it should be added that we are most grateful for their cooperation, forbearance, and care in not mutilating specimens.) In addition, interesting specimens from other Northwestern affiliated hospitals are sent to our laboratory. Perhaps it is because of this large volume of material that we are able to report such a relatively large number of broad ligament tumors. Be this as it may, we also believe that the frequency of such tumors, in anyone's experience, is directly related to his interest in the subject and thus how much or how well he looks for them. Certainly, unless one is interested, small grossly visible broad ligament tumors will be overlooked. Also, with the usual technique of cutting separate blocks of uterine tubes and of ovarian cortex, microscopic tumors will be missed. In addition, unless one is careful, it seems likely that large broad ligament tumors with ovary thinned and inconspicuously stretched out over their surface will be considered as ovarian cystomas or cystadenomas. We suspect that we have committed this particular sin ourselves. Unfortunately,

we also suspect that when cystadenomas or cystomas are sufficiently large and the ovary sufficiently stretched out or attentuated over the surface, it is not possible to determine their exact origin, i.e., broad ligament or ovary.

The present authors bear a grudge (or have a semantic block) against the Cohnheim theory of "embryonic rests" for the histogenesis of tumors. Fortunately this theory has been fairly well forgotten, except in the field of gynecologic pathology. Here the theory dies hard and probably persists because of human acceptance of "inverted" (or should it be "subverted") logic, e.g., "You can't prove I am wrong! Therefore I am right."

Nevertheless we hope that this presentation has demonstrated that there are numerous epithelial structures in the broad ligament made up of adult-type cells, from which tumors of epithelial type can be derived. Certainly there is sufficient fibrous tissue and smooth muscle tissue to explain the origin of fibromas and fibroadenomas.

We have intentionally omitted a discussion of the exact origin of our cystomas and cystadenomas. This must await further study; probably it involves the use of histochemical techniques. As a very tentative and probably hazardous "guess," it seems likely that cystomas and cystadenomas with both secretory- and ciliated-type cells are of mesonephric tubule origin. Those with nonciliated columnar epithelium probably are derived from the rete-medullary tubule complex. It is planned to study this subject in more detail.

The probable origin of certain others of these tumors has been mentioned in the text. It seems likely that the paramesonephric adenoma was of paramesonephric tubule or aberrant oviductal tissue origin. The rete adenoma had epithelium similar to, and was in direct continuity with, normal rete. It seems most specious to try to assign any other origin than rete to this tumor. Detailed evidence that the type of Brenner tumor presented here arose from rete has been presented elsewhere.[3]

It seems probable that the granulosa-theca-cell tumor arose from misplaced or accessory ovarian tissue. Postulation of any other origin seems like unnecessary gilding of the lily.

We can only speculate on the origin of the adenocarcinoma in the broad ligament. This patient had a most complete workup, so it seems unlikely that she had a primary tumor elsewhere, and that the broad ligament process was a metastasis. At one time, one of us (R. R. G.) thought that he was able to distinguish ciliated cells in this tumor, but more careful study with special stains has not confirmed this. The cells do have a peculiar "brush-border" appearance, however (Fig. 22). To our knowledge none of the epithelial elements normally found in the broad ligament has such "brush-border" appearance, although the overlying mesothelium (peritoneum) in properly fixed and carefully prepared specimens does have a very definite "brush border." It seems prudent not to guess further as to the exact progenitor of this adenocarcinoma.

Strangely enough, "mesonephromas" were not encountered, although we were working in the area where one could most expect to find them (granting that the origin of such tumors, if they exist as an entity, is actually from "mesonephric remnants or rests").

Conclusions

1. With such a variety of potential sources for tumor development, i.e., from the structures normally present in the adult female broad ligament, there is no need to revert to the Cohnheim theory of embryonic rests to explain the presence of true tumors in the broad ligament.

2. By the same token, it is surprising that true tumors of the broad ligament are relatively so uncommon. Perhaps many are not being recognized as such.

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Discussion

DR. ROBERT L. FAULKNER, Cleveland, Ohio.—The authors' presentation is the result of long-standing continued interest in the broad ligament. In addition to previous study of the embryology and anatomy of this region they have now reported their observations on a group of tumors occurring in this locality and in so far as possible commented upon their probable origin. It is amazing that 20 of their 27 reported tumors are varieties which are not in the common lists of broad ligament tumors, viz., serous cystomas and cystadenomas, Brenner tumors, and one granulosa-cell tumor. This is not to say that in view of the meticulous methods employed in their identification there can be much doubt of their proper classification. It simply means that most of us have not had the material or made use of it sufficiently to accumulate such a series.

Whether one has a special interest in the broad ligament or not, attention is forced in that direction on occasion by some of the bizarre carcinomas. I would like to ask the authors about the following case and to inquire if in their experience, or thinking, such a tumor could be of mesonephric-duct origin. A young woman of 34 presented herself with a draining vaginal sinus of 5 months' duration which was apparently connected with an indurated abscess cavity 8 cm. in the left broad ligament. Diagnosis had not been established. Guesses ranged from actinomycosis to carcinoma. Investigation of the uterine corpus and cervix was negative. Rather heroic biopsy of the broad ligament mass finally established the diagnosis of *epidermoid* carcinoma. She received no benefit from x-ray therapy and was finally operated upon with removal of the tumor mass which was entirely separate from the cervix or the uterus.

Our confusion arose, of course, because this was a moderately well-differentiated epidermoid carcinoma, almost certainly not of cervical or vaginal origin. Do the authors think that in the lower reaches of the mesonephric duct squamous carcinoma is occasionally possible, either from plaques of transitional or squamous epithelium already there, or through some process of direct or indirect metaplasia?

DR. ANDREW A. MARCHETTI, Washington, D. C.—This discussant is in complete agreement with the authors' semantic block against the Cohnheim theory of "embryonic

rests" for the histogenesis of tumors. Cells of embryonal rests do not preserve their undeveloped character. Generally they differentiate and acquire the features of adult cells. Adrenal gland cells which are found in the broad ligament (hilus of the ovary), for example, or the epithelial cells of the paramesonephric derivatives included in the broad ligament are as mature as their fellows in the normal adrenal gland and in the oviduct. The only thing abnormal about them is that they are misplaced.

Even with the historical affection which this discussant has for Wolff and Müller, he must acquiesce in the authors' insistence upon giving the structural derivatives in the broad ligament their histogenetic designation. In their thesis, it is the key to the clarification of the origin and the simplification of the classification of broad ligament cysts and tumors.

The authors were able to determine the derivation of 86 per cent of the 101 pedunculated and intraligamentary cysts which they studied. It was interesting to note that 90 per cent of the pedunculated and 40 per cent of the intraligamentary ones were identified as paramesonephric in origin. To average the combination, approximately two thirds then were of paramesonephric derivation. The combination of pedunculated and intraligamentary cysts in the remaining third were either of mesonephric duct origin or of mesonephric tubule origin, predominantly the latter.

There appears to be no argument against the manner in which the authors defined tumors of the broad ligament. Nor does one have to wonder why they were able to collect 27 tumors of the broad ligament. Among the 27 tumors which were classified, I am in accord with the interpretation which was placed on the probable origin of the 3 myomas, the 5 Brenner tumors, the rete adenoma, and the paramesonephric adenoma.

The origins of the granulosa-theca-cell tumor and the adenocarcinoma, I believe, were correctly based on speculation.

The 5 serous cystomas and the 9 serous cystadenomas whose exact origin "was most carefully omitted" in the discussion by the authors interested me most. The authors duly stated that further study must be given this subject. They did offer a very tentative and probably hazardous "guess" that the cystomas and the cystadenomas with both secretory- and ciliated-type cells are of mesonephric tubule origin. This discussant would like to presume upon the privilege by offering a more tentative and probably more hazardous "guess" than the authors. Based purely upon an impression and upon the preponderance of paramesonephric derivatives which the authors found among the pedunculated and the intraligamentary cysts of the broad ligament, it seems more likely to me that the cystomas and the cystadenomas will be found to be of paramesonephric origin.

DR. GARDNER (Closing).—Far be it from our group, who certainly do not shy away from the concept of metaplasia, to doubt that Dr. Faulkner's broad ligament epidermoid carcinoma could have originated through such change in cells of mesonephric origin.

Frankly, I would not have been surprised had the discussers taken me to task for "beating the drum" once more about our previously published classification of broad ligament "distention" cysts. Of this I have been guilty, and willfully so, since we believe that such a classification based on histogenesis is so logical, so proper, and so appropriate that we had hoped it would have been accorded wider acceptance by our contemporaries.

We carefully avoided a detailed discussion at this time about a probable origin for both serous cystomas and serous cystadenomas, because we believe that there are several additional factors to be taken into consideration about their genesis, and these have not even been mentioned in this paper. Certainly there is a possibility that such tumors may arise from the epithelium of the rete or of medullary tubules. Furthermore we have demonstrated that serous cystomas and serous cystadenomas are not always lined by a two-cell type of epithelium, and Dr. Marchetti re-emphasized this particular point in his discussion. Hence we refrained from expressing a definite opinion now about the origin of these particular broad ligament tumors. Further study is necessary, and we are in the process of making such investigations.

AN ANALYSIS OF 1,000 CONSECUTIVE MIDFORCEPS OPERATIONS*

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(From the Margaret Hague Maternity Hospital, Jersey City, N. J.)

THE obstetrical forceps have been in use for over 400 years and for most of that time have constituted the principal artificial means of relatively safe delivery of a living child through the maternal birth canal. For the past 70 years, cesarean section has gradually encroached upon the use of the forceps operation, generally to the betterment of fetal and maternal mortality and morbidity.

How extensive such a change should be with the hazards of cesarean section remaining greater than the hazards of vaginal delivery, particularly for the mother, apparently seems to be a matter of controversy in current obstetrical practice.

One thousand consecutive midforceps operations performed by at least ninety-six different operators were subjected to scrutiny in an attempt to determine the justification for the midforceps operation (Tables I and II). The operations classified as midforceps at the time of this study were defined: "When the vertex is engaged, and the biparietal diameter of the head is about at the level of the interspinous line."

TABLE I. PROFESSIONAL RANK OF OPERATORS

RANK	NUMBER	PRIVATE	CONSULTATION	NEONATAL DEATHS	STILLBIRTHS
Attending	9	303	74	2	6 (4)
Asst. Attending	17	165	66	3 (1)	3 (2)
Resident	33	144	91	8 (2)	4 (1)
Asst. Resident	23	63	26	0	0
Intern	14	16	1	0	0
Uncertain	0	11	8	0	2

TABLE II. SOURCE OF MATERIAL

Private		911
Consultation	266	
Clinic		74
Non-clinic		15

Analysis of Data

Fig. 1 indicates the comparative frequency of the various types of delivery at the time these operations were performed. The incidence of 1.9 per cent for midforceps represents about one half that of cesarean section. It is

*Presented at the Sixty-seventh Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Va., Sept. 6 to 8, 1956.

worth noting that the general policy of the staff of the hospital is to allow spontaneous evolution of labor, and "elective" forceps operations are not generally used for the termination of normal labor. Any forceps operation performed is generally done with the knowledge of at least one other staff member, and most such procedures have a reasonably legitimate indication.

There was one maternal death not related to the method of delivery, that of a patient moribund with a ruptured cerebral aneurysm who was delivered by midforceps in the interest of the fetus. The mother was comatose at delivery and died shortly thereafter; the infant lived.

Table III notes the indications for the midforceps operation. Six hundred eighty patients were nonparous and 320 parous prior to delivery. In each group the perinatal loss is noted. Dystocia generally meant deep pelvic arrest, but the records indicate frequent use of the term when "inertia" might be better employed. Inertia was used to indicate lack of uterine power in the absence of demonstrable arrest. Such separation is subjective and open to criticism and it might be more satisfactory to place both groups in one category.

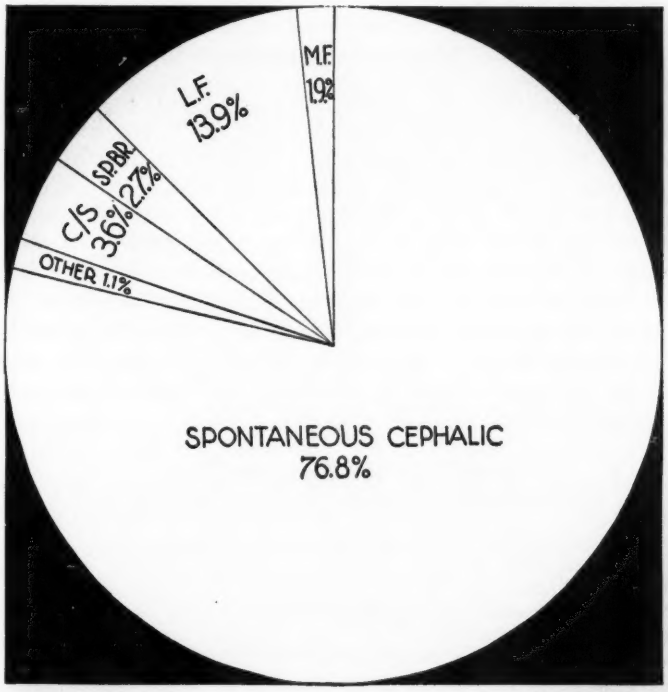

Fig. 1.—Comparative frequency of various delivery procedures during time of survey.

"Shorten second stage" was the designated indication when the situation warranted the assumption of early spontaneous delivery, but because of anesthesia forceps were often applied in multiparous women when the vertex was still in a transverse position.

"Teaching" was used in the same circumstance to allow the resident staff to apply instruments on heads either in the transverse or posterior positions.

"Fetal distress" usually was diagnosed when the fetal heart tones were over 160 per minute or under 100 per minute with or without observation of meconium. Generally, involvement of the cord rather than dystocia was anticipated at application.

The staff generally is not committed to routine repeat cesarean sections and feels that cases in which vaginal delivery is anticipated should have the second stage of labor shortened as much as possible. Whether a midforceps operation in such situations is defensible is doubtful.

Prolapsed cord occurred in a few cases in which the operator judged delivery faster by forceps than by cesarean section because of the time consumed in preparation for the latter.

TABLE III. INDICATIONS

		NEONATAL DEATHS	STILLBIRTHS
Dystocia (all)	670	7	5
Shorten second stage	179	3	4
Fetal distress	71	1	5
Prior cesarean section	26	0	0
Teaching	21	1	0
Inertia	20	1	0
Abruptio placentae	8	0	0
Prolapsed cord	5	0	1

Maternal Morbidity

The maternal morbidity in terms of birth-tract injuries is numerically large (Tables IV and V). There were 25 fourth-degree extensions (complete perineal tears), 35 third-degree extensions (tears of either the sphincter muscle or the rectal mucosa but not both), and 40 second-degree extensions. In this apparently large group of extensions there was one case of postpartum hemorrhage. Fifty-four of these infants exceeded 3,500 grams in weight. One of the three clinical divisions and several of the attending obstetricians perform routine median episiotomies in all vaginal deliveries, believing the anatomical results to be superior to those of the mediolateral variety, even at the risk of extension which causes little if any extra trouble if properly repaired. Such judgment, though perhaps arguable, appears justified because all such extensions healed satisfactorily.

TABLE IV. MATERNAL MORBIDITY

Perineal injury		100
4° Extension	25	
3° Extension	35	
2° Extension	40	
54 infants exceeded 3,500 grams in weight		
Cervical lacerations repaired		29
19 infants exceeded 3,500 grams in weight		
23 forceps rotations		
Vaginal extension of episiotomy		162
62 infants exceeded 3,500 grams in weight		
None of foregoing required additional hospitalization		
Blood loss exceeded 500 c.c. in 23 instances		
Bladder injuries, vesicovaginal fistulas		3
Repaired successfully immediately	2	
Repaired 6 months post partum	1	
All occurred with rotation with Kielland forceps		
All occurred in the hands of one operator		
Ruptured uterus		1
Prior cesarean section for abruptio placentae, fetal distress. Rupture probably occurred prior to operation and caused the distress		
Fracture of coccyx		1
Foot drop		1

TABLE V. MATERNAL MORBIDITY NOT RELATED DIRECTLY TO OPERATION

Perineal abscess		1
Hematoma of perineum		1
Dehiscence of episiotomy		1
Uterine atony with hysterectomy		3
Hours post partum	1	
10 days post partum	1	
44 days post partum	1	
Endometritis		40
Mastitis		2
Pyelitis		3
Cystitis		2
Aspiration pneumonia (mild)		1

There were 29 cervical lacerations with 7 postpartum hemorrhages; 19 infants exceeded 3,500 grams in weight and forceps rotation was used in 23 instances. The cervix is inspected routinely after midforceps operations, and it is conceivable that some of these lacerations which did not cause hemorrhage would otherwise not have been noted.

Vaginal extension of episiotomies occurred in 162 instances with 15 postpartum hemorrhages; 62 of the infants exceeded 3,500 grams in weight. Many of these extensions were of minor importance and were diagnosed by conscientious house officers who were required to describe the operations fully.

Bladder injuries had serious consequences in 3 instances of vesicovaginal fistula. Two of these were repaired successfully at the time of delivery, and the third was repaired six months post partum, also successfully. All 3 fistulas occurred during the course of rotation and delivery with Kielland forceps in the practice of one operator, during a rather short period of time, and presumably were due to some error in technique which has not recurred.

One rupture of the uterus occurred through the scar of a previous cesarean section before the application of forceps, which was done for fetal distress, but too late to save the infant.

Three hysterectomies were performed post partum for uterine atony, one a few hours, one ten days, and the third forty-four days post partum. How necessary they were is a matter of conjecture but the records do not indicate any relation to the means of delivery.

Other maternal morbidity, probably not directly related to the means of delivery, included instances of endometritis, pyelitis, mastitis, cystitis, aspiration pneumonia, perineal abscess, perineal hematoma, and dehiscence of episiotomy and foot drop.

Perinatal Mortality

The total fetal wastage was 2.8 per cent—1.5 per cent stillbirths and 1.3 per cent neonatal deaths (Tables VI, VII, and VIII). They are listed in detail with what appears to us to be a reasonable separation into three groups. First, those infants who were stillborn or who died after birth and whose deaths appear directly attributable to the method of delivery; second, those whose deaths may have been due to the method of delivery; and third, those who would not have survived no matter how delivered.

At least twelve infants (1.2 per cent) probably would have lived if their mothers had been subjected to cesarean section or the particular operators had been more facile or experienced in the use of forceps. Whether such errors were in technique or judgment is not resolvable in all instances.

TABLE VI. PERINATAL MORTALITY

Total hospital perinatal mortality Neonatal 18 per 1,000 Stillborn 16 per 1,000	34 per 1,000 live births
Midforceps only, perinatal mortality Neonatal 13 per 1,000 Stillborn 15 per 1,000	28 per 1,000 live births

TABLE VII. NEONATAL DEATHS

WEIGHT (GRAMS)	OPERATOR	HOURS OF LABOR	HOURS MEMBRANES RUPTURED	HOURS OF SECOND STAGE	STATION OF PEAK OF VERTEX AT OR BELOW LEVEL OF ISCHIAL SPINES (CM.)	POSITION	TYPE OF FORCEPS	CAUSE OF DEATH
2,390*†	Resident	20	6	1	2+	FT	Kielland	Intracranial injury
3,800	Asst. attending‡	16	7	1	2+	OT	Kielland	Intracranial injury
5,100	Resident	16	13	1	2+	OA	Dewees	Intracranial injury
3,912	Resident	11	4	7	1+	OT	Kielland	Intracranial injury
3,590	Asst. attending	15	8	7	2+	OA	Dewees	Rupture of liver
2,350	Resident	8	1	1	2+	OT	Kielland	Intracranial injury
3,090	Attending‡	3	5	1	3+	OP	Kielland	Unknown
2,090*†	Resident	50?	54	5	1+	OA	Dewees	Atelectasis
3,700	Resident	9	4	2	1+	OP	Kielland	Severe congenital heart anomaly
2,900	Resident	14	10	?	2+	OA	Dewees	Multiple congenital anomalies
2,980†	Attending‡	3	0	1–	2+	OA	Kielland	Toxoplasmosis
2,025	Asst. attending‡	8	1	1–	1+	OA	Tucker-McLane	Severe congenital heart anomaly
1,520†	Resident	9	4	3	?	OT	Kielland	Cyclops, etc.

*Twins.
†Multipara.
‡Board certified.

Sixteen infants were lost in the nonparous group, 12 in the parous women.

There were 12 sets of twins in the series. Three of the infants died neonatally; one had a severe congenital defect, the other two weighed less than 2,500 grams, one of whom presented as a brow and died of intracranial injury; the other died of atelectasis after prolonged labor.

It is perhaps worthy of note that 4 of the 5 infants who succumbed to intracranial damage were delivered by personnel of limited experience.

TABLE VIII. STILLBIRTHS

WEIGHT (GRAMS)	OPERATOR	HOURS OF LABOR	HOURS MEMBRANES RUPTURED	HOURS OF SECOND STAGE	STATION OF PEAK OF VERTEX AT OR BELOW LEVEL OF ISCHIAL SPINES (CM.)	POSITION	TYPE OF FORCEPS	TIME AND CAUSE OF DEATH
5,030*	Resident	13	8	3	2+	OT	Kielland	Intra partum: Impacted shoulder
5,160*	Resident	15	25	5	2+	OT	Kielland	Intra partum: Impacted shoulder
4,800	Attending†	20	48	4	2+	OT	Kielland	Intra partum: Tight cord?
3,560*	Attending†	9	11	4?	2+	OA	Dewees	Intra partum: Ruptured uterus
3,580	Asst. Attending†	22	19	6	2+	OT	Kielland	Intra partum: ?
3,200	Resident	18	18	2	2+	OT	Kielland	Intra partum: Pitocin?
5,239*	Resident	7	0	1	2+	OP	Dewees	Intra partum: Maternal diabetes
3,250*	Attending†	8	8	1	0	OA	Dewees	Intra partum: Prolapsed cord
3,600*	Attending†	37+	16	2	2+	OT	Elliott	Ante partum: Atelectasis
3,320	Attending†	14	12	1	0	OT	Dewees	Ante partum: Craniotomy
2,420	Asst. Attending†	16	3	1	2+	OA	Dewees	Ante partum: ?
2,[illegible]00*	Resident	7	0	1–	2+	OA	Dewees	Ante partum: Torsion cord
3,830*	Resident	4	4	1	2+	OT	Kielland	Ante partum: Tight cord
3,680	Asst. Attending†	13	38	1	3+	OA	Kielland	Ante partum: Maternal diabetes, etc.
2,700	Attending†	23	48	7	2+	OP	Kielland	Ante partum: Tight cord

*Multipara.
†Board certified.

In all but one instance the hours of labor were within average limits, and in 9 of 13 instances the station of the head would classify the operation as of the "low-mid" variety.

Seven infants who died subsequent to birth were subjected to a forceps delivery because of arrest, 4 such deaths being due to intracranial injury.

The stillborn infants died of a variety of causes. From the preventive standpoint the most important cases were those of 2 oversized infants of

multiparous women who died during attempts to free impacted shoulders. The labors of these women were of average duration and they had ample gynecoid pelves, but could not deliver infants of over 5,000 grams.

The other factor that caused deaths intra partum was fetal distress during the second stage of labor. When such distress is noted in a multipara with a fully dilated cervix it is usually more expedient to deliver the infant by extraction through the birth canal than to subject the mother to cesarean section, when it is problematical whether the operation will actually be in time to save a compromised infant. Until the causes of such distress are more readily and accurately diagnosed some infants will be lost.

Such factors as the length of labor, the length of time the membranes were ruptured, the length of the second stage of labor, the weights of the infants delivered, and the anesthetic agents used for delivery have all been studied in relation to the neonatal deaths and stillbirths. None of these seemed to have an effect on perinatal loss.

Pitocin

The use of posterior pituitary extract to combat inertia and even minor degrees of disproportion is becoming a common obstetrical procedure, in addition to its even greater use for the induction of labor.

Labor was induced in 38 (3.8 per cent) of the patients in this series with Pitocin, labor was stimulated in 110 (11 per cent) additional patients with Pitocin, generally but not always by the intravenous technique. While the general opinion of the staff is that the use of Pitocin occasionally avoids the necessity for cesarean section, the relatively large percentage of patients who were finally subjected to forceps delivery, which could be more traumatic to the infant than suprapubic delivery, leaves some doubt as to its desirability if there is any question of even a minor degree of disproportion in a particular case. It is not reasonable to stimulate labor in a borderline case to the point of engaging the vertex, if the augmented uterine forces are still unable to produce spontaneous delivery. There was one instance in which Pitocin was held responsible for a stillbirth in which fetal distress was first noted during the administration of the drug.

Application of Forceps

Eight hundred eighteen (81.8 per cent) forceps applications were performed with the peak of the calvarium 2 cm. or more below the interspinous line (low midforceps). Twenty-three cases of fetal loss occurred in this group, the remaining 182 (18.2 per cent) cases of application at higher stations accounting for the loss of 7 infants (midforceps).

The percentages are not significant but tend to indicate that the higher application increases fetal hazard.

Type of Forceps

Ten varieties of forceps were used in this series of operations (Kielland, Dewees, Barton, Elliott, Tucker-McLane, Piper, Hodge, Tarnier, Hawks-Dennen, and Luikart). Generally the Kielland instrument was used in transverse and posterior positions for rotation and extraction, and the Dewees axis traction instrument for extraction in anterior positions. The instances of the use of manual rotation, Scanzoni maneuver, or multiple application rotation (''key-in-lock'') were insignificant in number.

Usually the Kielland forceps were applied in the classical manner described by the inventor for transverse positions and in the inverted position for posterior positions. In all cases the aim was to accomplish cephalic application.

The Dewees forceps were likewise applied and axis traction accomplished in the fashion outlined in standard textbooks. Whether the use of other instruments would have greatly changed the results cannot be determined.

There were 8 (0.8 per cent) instances of trachelotomy prior to application of forceps, all with satisfactory results. The majority of the staff considers Dührssen's incisions seldom if ever indicated.

Comment

This series of operations has been presented to indicate the results of the use of forceps at levels of the pelvis between engagement of the vertex and its presence on the perineal floor. There is no unanimity of opinion concerning the classification of the use of forceps according to the position of the head in the birth canal. The use of high forceps is generally defined as the application on an unengaged vertex that is not "floating." Low forceps is beginning to be defined as the application of the instrument when the vertex is on the perineum and visible between contractions, sometimes with the additional stipulation that the sagittal suture should be in the anteroposterior diameter. Between these two, e.g., high and low forceps, lies the greatest distance traversed by the head in its journey through the pelvis. Between a head which is just engaged and one on the perineum is a large area of greatly differing values relative to the ease of forceps application, rotation, and extraction. This distance of passage within the pelvis is too great to be defined as a single operation.

Theoretically a classification into four planes, as suggested by Dennen, is ideal. Practically there are some objections. If more than one criterion is used for the definition by clinical examination, there can be instances where each factor may place the head at a different level. While it is generally true that when the leading portion of the calvarium is at the interspinous level the head is engaged, and while it is also generally true that when the leading portion of the calvarium is 2 cm. or more below the interspinous line the biparietal diameter of the head is about at the level of the ischial spines, it is not always specifically true. Unfortunately, the variation in relationship between the levels of the leading portion of the calvarium and the biparietal diameter of the fetal skull occurs in precisely those cases in which the use of instrumental delivery is most often considered. Dennen is aware of this in stating that in cases of extreme molding, abnormal attitudes, and in deformed pelves, the presumed biparietal diameter should automatically be placed at the next higher plane than the one indicated by the level of the leading point. This appears to negate the use of dual criteria, since it fails when most needed.

It is suggested that the level of the leading point of the calvarium exclusive of caput be the single factor used in determining the type of forceps operation, and the leading point be defined in relation to the interspinous line.

Under ideal conditions, x-ray facilities provide the only real knowledge of the position of the biparietal diameter of the head, which is the single factor which really concerns the obstetrician. If it were possible everywhere to have x-ray facilities around the clock, there would be no excuse for the application of

any forceps in the midpelvis without exact knowledge of the pelvic architecture and the position and level of the head. A lateral film, in the standing position if feasible, would be adequate; a complete pelvic estimation would be ideal.

There is ordinarily no satisfactory objective method by examination only to determine the position of the biparietal diameter. Some estimate may be made by palpation of the amount of the fetal skull above the symphysis with an intravaginal hand, allowing the operator to make a subjective estimation, but the results of such examination depend too much on the experience of the operator to be subjectively transferable.

We would recommend this subject to the attention of pertinent groups whose findings would be generally followed throughout the country, as have standards of morbidity, prematurity, and similar subjects. Until such time as the specialty has such criteria, statistical papers such as this on ill-defined subjects have no comparative value. This is the principal reason there is controversy over the midforceps operation.

The present study gives little information concerning forceps operations when the presumed level of the biparietal diameter of the fetal skull is above the interspinous line. We believe the application of forceps under such conditions is hazardous, and moreover further believe that, without x-ray evidence, many such applications are on fetal heads that are not yet engaged, particularly when the labor or second stage has been prolonged.

Very often the error in such "difficult" forceps operations is based upon a fallacious estimate of fetal size. Too often it is presumed that the fact of a prior vaginal delivery of a normal-sized infant means invariable vaginal delivery of subsequent infants, with the attempt made so to deliver oversized infants by instrumental means. We are finding more and more instances of the necessity of suprapubic delivery in such cases and have no qualms about occasionally subjecting a multiparous woman to primary cesarean section for dystocia in the presence of normal pelvic architecture.

Our general impression has always been that any forceps applied in the midpelvis has been a "trial" forceps operation, in the sense that we would have no hesitation in removing them and performing cesarean section if we encountered undue difficulty. Experience generally will show such instances to be quite few, but it is our impression that the introduction of the term has allowed some operators to desist in difficult operative attempts without having their judgment criticized, where previously they might have persisted in thinking that once forceps were applied they were committed to delivering the infant forthwith.

Despite some of the foregoing comments we believe the midforceps operations, used when the vertex is deeply engaged and the biparietal diameter of the fetal head is presumably about at the level of the ischial spines, is the method of choice for delivery in a small group of cases where inertia, or faulty mechanism of labor, causes arrest after adequate but not prolonged trial of

the effects of the maternal forces. This is particularly true in primiparous women because of the unquestioned effect on, and the inherent dangers in, subsequent childbearing occasioned by cesarean section.

Summary

Statistics are presented on 1,000 consecutive operations of forceps applied in the midpelvis, with some comments on the description of the operation and the use of the procedure in modern obstetrical practice.

In our opinion the results justify the continued use of the midforceps operation and the instruction of house officers in its proper techinque in the small group of instances in which we feel the procedure is indicated.

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Discussion

DR. E. H. DENNEN, New York, N. Y.—The excellent end results in this presentation constitute a convincing argument for the negative side of the controversy of cesarean instead of midforceps.

The incidence of midforceps of 1.9 per cent in Dr. Cosgrove's form of classification of the operation is extremely low. Especially so, since many of those in the lower half of the pelvis might *not* have been listed as midforceps under some other forms of classification. In all probability the incidence in general is being reduced by the use of Pitocin. In selected cases of true inertia, Pitocin is indicated, but in certain cases of deformed pelvis or malposition its use has been followed by disaster.

With no maternal deaths, the perinatal mortality of only 2.8 per cent, is so low that I suspect that Dr. Cosgrove was pleasantly surprised by his own findings. Nevertheless, this did not deter him from trying to determine those deaths which might have been avoided. Twelve, or 1.2 per cent, were classed as such. This is a small figure for such a large series of cases attended by some 96 different operators with varying degrees of experience and skill.

Most of the troubles accompanying a midforceps operation follow errors in diagnosis of the shape, position, station, and attitude of the fetal head and the type of pelvis, plus a limited knowledge in the choice of instrument to suit the case. The type of pelvis is the factor least emphasized in most forceps discussions, but it is the most important one in deciding on the choice of instrument.

If one depends only on the level of the leading bony point of the head, to diagnose station, he will be wrong most of the time, especially if the head with considerable molding is posterior and the pelvis is android in type. Here, it is necessary to have more than one criterion for diagnosing the correct station. In such a case, with the leading point at the

level of that of the average low-mid head, the biparietal diameter is at a higher level—in reality—mid or occasionally high; and the higher the head the more difficult and more dangerous the operation.

Such knowledge should cause the operator to hesitate before attempting it without more exact information. This calls for an x-ray, at least a lateral view to show the station and type of sacrum. From the information gained he may decide to do a cesarean section. If not, the choice of instrument is the Kielland, which, with its advantages of application, flexion and rotation, without displacement, favors better results with less manipulation and more finesse than do other types. On simpler cases, especially those in which the pelvis is not a factor, any of the other methods of manual or instrumental rotation with which one is familiar and which one prefers may be used. Not infrequently the superiority of the Kielland has been demonstrated by success after failure with other methods on the same case. The same holds true for the anthropoid pelvis with an occiput posterior, unless there is insufficient room to permit anterior rotation. Then the delivery is done as a posterior with a Simpson type of forceps with axis traction. The Dewees is popular in our area. A similar type fits best when the occiput is anterior, regardless of the type of pelvis, if molding is present.

When the deformity of the pelvis is in the sacrum, shortening the anteroposterior diameter of upper or midpelvis, and the vertex is transverse with or without asynclitism, the Barton forceps stand alone as the choice of the instruments in common use. They are specially constructed to give application and traction safely with descent in the required transverse to the outlet before anterior rotation is done. Here the Kielland and classical instruments are a hazard, since with them the required traction in the transverse because of the short anteroposterior endangers the symphysis, bladder, cervix, vagina, and fetal head. Similar contraindications hold for the Barton in android and anthropoid pelves, requiring descent in the anteroposterior diameter.

An accurate knowledge of the pelvis seems to be sufficiently important to justify establishing x-ray facilities for obstetrics around the clock, even if only for a lateral view.

A midforceps delivery can be extremely dangerous, especially when the case is poorly selected and the operation poorly executed. However, this is not sufficient reason to discard a valuable procedure which, when certain conditions are met, can produce satisfactory results, such as those shown by Dr. Cosgrove and others.

Our results have been presented previously; to this Society in 1952 and elsewhere.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—The doctor who has never made a mistake has either not practiced, keeps no records, or has an unreliable memory. Most doctors who practice obstetrics have caused intracranial injury. If we were fortunate the baby died; if not, it lived as a constant reminder, in most instances, of an error in judgment on someone's part. We are all proud of our follow-up for cancer, various gynecologic operations, toxemia and so forth, but, so far as I know, there is no report of anyone following up all of the babies delivered by him or on his service to determine just how good or how bad was the art of obstetrics employed.

I wish to discuss three additional points: perinatal mortality, skill, and "trial forceps."

I classify as a midforceps any delivery in which the baby's head is within 1 cm. of the spines. If it is more than 1 cm. above I call it a high forceps. If I have to "fish" I call it a floating forceps. I disregard the level of the caput which can be 1 to 4 cm. in thickness. The perinatal mortality rates reported by the author, by us, and by six other obstetricians indicate that there are fewer babies lost if born by midforceps than for the hospital as a whole. This does not make sense.

I believe there is a very definite place for the use of midforceps provided the obstetrician is skilled in their use. As I emphasized in a report two years ago, the only way in which one can become skilled and maintain that skill is by constant practice. The author reports one thousand midforceps by 96 different operators; approximately 10 forceps operations per man. However, midforceps operations comprise 12 per cent of their total

forceps incidence; for 77 per cent of their babies were delivered spontaneously. Compare these data, for example, with our service where in a representative two years midforceps comprised 2.7 per cent of our total 67 per cent incidence of forceps.

In the accompanying table I am presenting four periods over a twenty-five-year interval. The number of midforceps operations remains constant until the last four years and I question the accuracy for I believe that some of our midforceps were classified as low forceps. Note that the percentage of total forceps has constantly increased until over two-thirds of our deliveries are by forceps, the majority being low and outlet but they do permit the residents to gain some skill in their use.

TABLE I. MIDFORCEPS

	1931	*1938-1940*	*1946-1948*	*1952-1956*
Number	99	173	160	137
Incidence (%)	5.0	3.2	2.0	1.0
Stillbirths (%)	4.6	3.0	2.3	0
Neonatal deaths (%)	2.8	5.0	0	1.5
Birth injury, fatal	1	1	1	1
	1931-1940	*1941-1945*	*1946-1950*	*1952-1956*
Total stillbirths	1.9	1.3	0.9	1.16
Neonatal deaths (%)	1.7	1.3	1.1	1.05
Birth injury (%)	0.53	0.12	0.09	0.1
Midforceps per cent of total forceps	16.0	10.0	2.7	1.5
Cesarean section (%)	3.9	4.7	4.9	5.0
Perinatal mortality for 1,000 grams +				

We insist upon the residents using just one type of forceps. We grant that there are certain forceps that are fitted for positions of the head but are they always available and does the man have experience in their use?

"Trial forceps" should be condemned. When the patient has been in labor long enough to attempt a delivery, the baby is already in jeopardy. A trial pull does not improve its chances of survival. All of us have delivered babies by cesarean section after prolonged labor and although the fetal heart tones were normal before operation and the baby was born with a normal heart rate, yet it did not survive. Furthermore, cesarean section after trial forceps increased the hazard for the mother despite antibiotic therapy. If the obstetrician has not had sufficient experience to evaluate the pelvis and fit of the baby's head with all of the methods that are available, and requires a trial forceps to determine whether or not he can deliver the baby by vagina, he is lacking in the art of obstetrics and should call a consultant.

DR. J. BAY JACOBS, Washington, D. C.—It is difficult to classify forceps operations unless one does have x-ray evidence of the station of the head in relation to the anatomy of the pelvis. The lateral pelvic roentgenogram, taken in the standing posture, gives us that information very definitely in two out of three cases because that is the frequency in which the biparietal diameter presents in the true conjugate. With this roentgenogram one can readily note the architecture and depth of the pelvis and the length and the architecture of the sacrum.

We used to be told that when the biparietal diameter was in the true conjugate, the lowermost portion of the head could be expected to be at the ischial spines and the head was then engaged. There is of course a great variation in the depth of the pelvis and, in many cases, even though there is no molding of the head, the lowermost portion may appear to be well above the ischial spines, giving the impression that the head is not engaged. You would then be surprised to find on lateral roentgenography that the biparietal diameter has entered the brim or might be below the inlet of the pelvis. Then, where the woman has been in labor for some time, we must realize that there is a certain degree of molding or elongation

of the head, as well as a certain elongation due to caput. For an accurate determination of the type of forceps delivery in relation to the station of the head, one should have a lateral pelvic roentgenogram. Such facilities should be available in any hospital twenty-four hours a day.

I hesitate to disagree with Dr. Dennen but I do not feel as strongly as he does regarding the importance of using a certain type of forceps for each individual case. I am inclined to feel as Dr. Dieckmann does that with any average case one can manage the situation very well with a certain type of forceps. Personally, I prefer Simpson forceps.

DR. COSGROVE (Closing).—Eleven per cent of these patients whose pregnancies were terminated by midforceps operations had their labors stimulated by pituitary extract. We have noted, even on our own staff, some degree of enthusiasm for using the drug as a substitute for midforceps. To us it is unreasonable to use an oxytocic to get the head through the inlet and think it would be better if such labors were not stimulated at all.

We have attempted to estimate what happened in each type of pelvis that necessitated these operations, but there are over 200 general practitioners in our hospital who do not do midforceps operations at all but who do deliver babies. Very frequently the consultant sees patients of these individuals without any information concerning the type of pelvis.

I do not want to disagree with Dr. Dennen on how to classify this operation. I simply wish that someone or some group would provide a classification that everyone could and would use so we would all know what we were talking about.

Most of the instruments used were either Kielland's for rotation or Dewees' for extraction. Although there were actually ten different types of forceps used, most were used very rarely.

I thoroughly agree that the figure for perinatal loss with midforceps gives a false impression when compared with the total perinatal losses. It excludes all of the prematures, all cases of severe abruptio placentae, and all placenta previas, that compose the general perinatal mortality.

I am not sure just where I stand in relation to teaching the men forceps. At one time most of our deliveries were elective low forceps. Then we stopped for some years and I think perhaps we are now doing more again, principally for teaching. The actual number of midforceps per individual was a lot less than ten. Most were done by a relatively small group, so many of the operators did only one or two. Sometimes a man goes through our residency doing very few.

CHANGES IN CHORIONIC TISSUE OF ABORTED PREGNANCY*

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THE sporadic recognition of both gross and microscopic evidence of molar change in abortion specimens in the past few years has created an interest in the frequency and possible etiological relationships of this condition. The literature contains few specific references to these changes with the exception of the early reports of Mall and Meyer[1, 4] and Hertig and Edmonds.[2] It appears that little clinical significance is attached to such changes and that only occasional note is made of early molar change by pathologists.

It was consequently thought that an additional study of early abortion specimens would be of some value. It appeared that the concept of molar change of the placenta was anything but precise and perhaps depended upon the preconceived ideas of the pathologist examining a given specimen.

As a means of establishing some general histologic criteria of molar change in the chorionic tissue being examined in the laboratories of the Indiana University Medical Center and the Indianapolis General Hospital, a systematic review was undertaken. From Jan. 1, 1954, to Dec. 30, 1955, all of the abortion specimens were reviewed and carefully examined. No special attention was directed to the fetus during this period of time. Of a total of 188 specimens examined, 38 (20.2 per cent) showed molar change of the placenta by our criteria.

This phase of the study resulted in our establishing criteria of the changes that we feel should be demonstrated in the chorionic villi to justify the diagnosis of molar change. These are:

1. Avascular or relatively avascular villi.
2. Edema of the stroma with or without increase in size of the villi with the development of cystic spaces which tend to coalesce.
3. Proliferation of trophoblastic cells in excess of the usual two-cell layer in at least some of the villi excluding the anchoring villi. These findings should be seen in several villi in the specimen.

With the use of these criteria, a specimen was considered to show molar change when all three of these variations from normal were present. When two of the criteria were satisfied or when one was present with the other two questionably demonstrated, the specimen was classified as showing questionable molar change.

All of the abortion specimens since Jan. 1, 1955, have been interpreted by these criteria.

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During the 18 months until July 1, 1956, all consecutive abortion specimens have been carefully examined. A total of 314 specimens have been received and, of these, 90 specimens have been considered to be intact. Only those specimens that were complete beyond a reasonable doubt were included in this series.

A specimen was considered complete when the chorion was not ruptured or, if a rent was demonstrated in the chorion, the presence or absence of a fetus was felt assured. The specimen with an unruptured chorion was obviously wholly complete. Such an intact specimen is illustrated in Figs. 1 and 2 and represents the unruptured chorion of a 13 weeks' gestation. Additional information obtained for each specimen was that of the age, race, gravidity, and parity of the patient and the duration of pregnancy in weeks from the last menstrual period to the date of abortion.

Fig. 1.

Fig. 2.

Fig. 1.—Specimen received intact. (×1½; reduced ¼.)
Fig. 2.—Same as Fig. 1 after opening, revealing a cylindrical fetus. (×1½; reduced ¼.)

Dissection of the specimen under the dissecting microscope with magnification up to 100× disclosed the presence or absence of an amniotic sac. This was not always satisfactorily determined. The fetus was classified after Mall (modified) as being (a) absent, (b) nodular (Fig. 3) in that there was definite fetal tissue, oval or nodular in shape but with no recognizable fetal parts although subsequently histologically confirmed undifferentiated fetal tissue, (c) cylindrical (Fig. 2) elongated in shape (unorganized), continuous with a recognizable umbilical cord but with no fetal parts grossly identifiable, (d) stunted or deformed with the crown-heel length of the fetus not corresponding to the calculated gestational age or showing gross deformity, and (e) macerated.

The formalin-fixed specimen was also suspended in water and the villi teased apart under the dissecting microscope (Fig. 4). Villi were obtained

Fig. 3.—Specimen received intact after opening, revealing a nodular fetus.

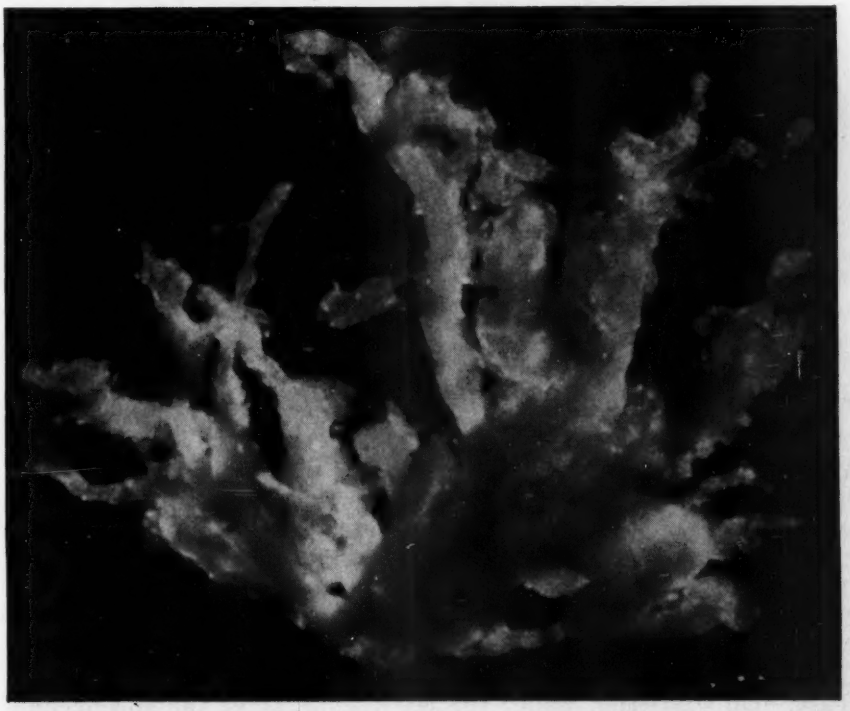

Fig. 4.—Appearance of normal villi suspended in water. (×12½; reduced ⅛.)

from the chorion frondosum and an impression recorded of the character of the villi as to caliber and the presence of large terminal distended vesicles. The villi were transilluminated to determine lack of stromal substance. It was possible to note the termination of the villus vessels and occasionally to identify cystic villi distal to this. Such cystic distal villi were encountered where there was an increase in the caliber of the villus stalk. The specimen shown in Fig. 5 was from a 24-year-old white woman, para 0, gravida i, whose last menstrual period was Sept. 15, 1955, and who aborted spontaneously on Nov. 20, 1955, at 9 weeks' gestation. On examination of the specimen under the dissecting microscope, the chorion was intact and upon opening the chorion and amnion the fluid was clear. No fetus was demonstrated. On suspension of the villi obtained from the chorion frondosum, the distal portions of the villi were bulbous and the caliber of the villus stalk was increased. Histologically, the villi were avascular (Fig. 6). There were cystic spaces present which tended to coalesce and the chorionic epithelium was more than two layers thick.

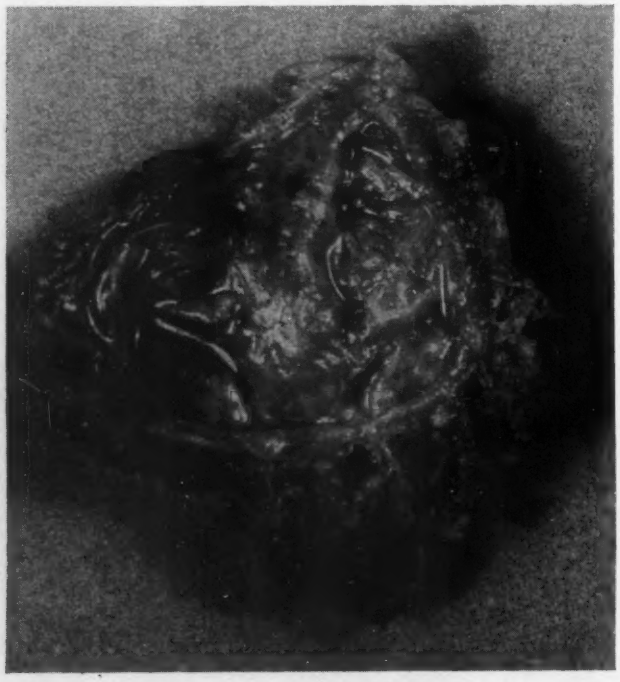

Fig. 5.—Intact specimen after being opened, containing no fetus. (×3; reduced ⅕.)

The average age of the patients from whom specimens were studied was 26 years. The average parity and gravidity were 2.1 and 3.7, respectively.

A blighted conceptus was found in 68 of the 90 specimens (76 per cent) (Table I). Of these, 9 were absent, 12 were nodular, 16 were cylindrical, 22 were stunted, and 9 were macerated. In no specimens in which unquestioned molar change was demonstrated was there a normal fetus; all were pathologic conceptuses. The group of specimens questionably demonstrating molar change was associated with four abnormal and three questionably abnormal fetuses.

The amniotic fluid in 14 of the specimens was clear and in 4 was noted to be bloody. On dissection under the microscope 11 of the specimens showed villi that were distended and bulbous and in all but 3 of them all the histologic

criteria of molar change were seen. Eleven of the 34 specimens showing molar change were suspected by examination of the villi with the aid of the dissecting microscope.

TABLE I. BLIGHTED CONCEPTUSES

	NOT MOLAR	MOLAR	QUESTIONABLE MOLAR	TOTAL	% MOLAR AND QUESTIONABLE MOLAR
Absent	3	6	0	9	67
Nodular	4	6	2	12	73
Cylindrical	6	6	4	16	59
Stunted	13	7	2	22	45
Macerated	6	2	1	9	33
Total	32	27	9	68	53

In 8 specimens the polarity of the attachment of the umbilical cord to the chorionic plate was lost and in 3 of them the histologic appearance was that of molar change.

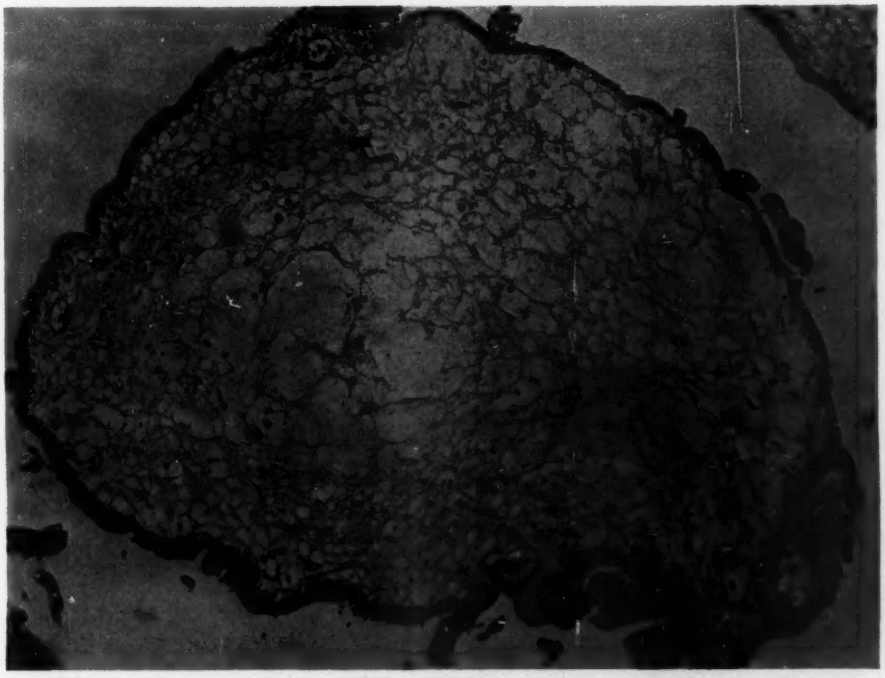

Fig. 6.—Histologic appearance of villi from specimen illustrated in Fig. 5. (×150; reduced ¼.)

Molar change was not demonstrated in 3 missed abortuses. Twin abortuses were encountered 5 times (Figs. 7 and 8) and two of the specimens showed molar change. One specimen was from a criminal abortion and molar change was not demonstrated. Only one specimen was from a patient who aborted habitually and molar change was demonstrated. The only previous specimen from this patient available in this laboratory showed insufficient chorionic villi to determine whether molar change was present and no mention was made in the previous episode of the presence or absence of the fetus.

Comment

From the period of study during which a detailed examination of the specimen in its entirety was made, it is apparent that an accurate interpretation can be made concerning the presence of a pathologic fetus. Reasonable

assurance is possible that the specimen is intact. Suspending the villi in water gives an impression of the size of the villi but we were not able to predict with certainty that all of our criteria for molar change would be present histologically. The finding of a pathologic conceptus is an indication that the subse-

Fig. 7.

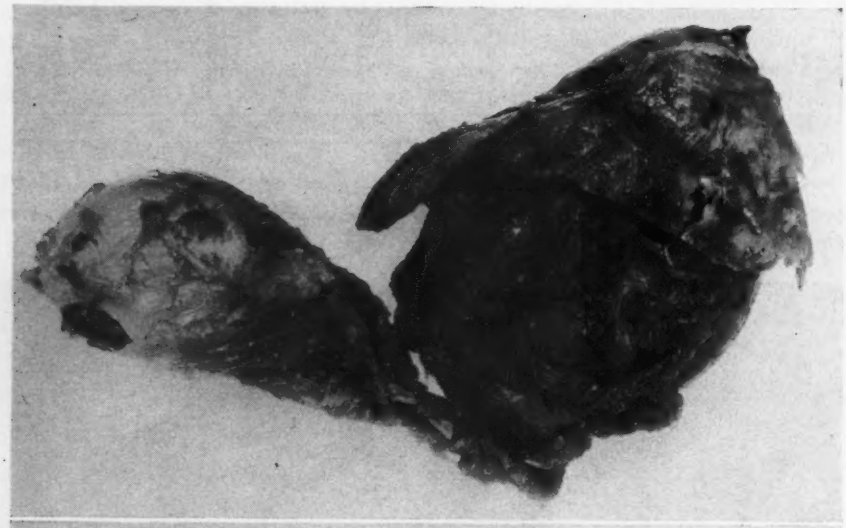

Fig. 8.

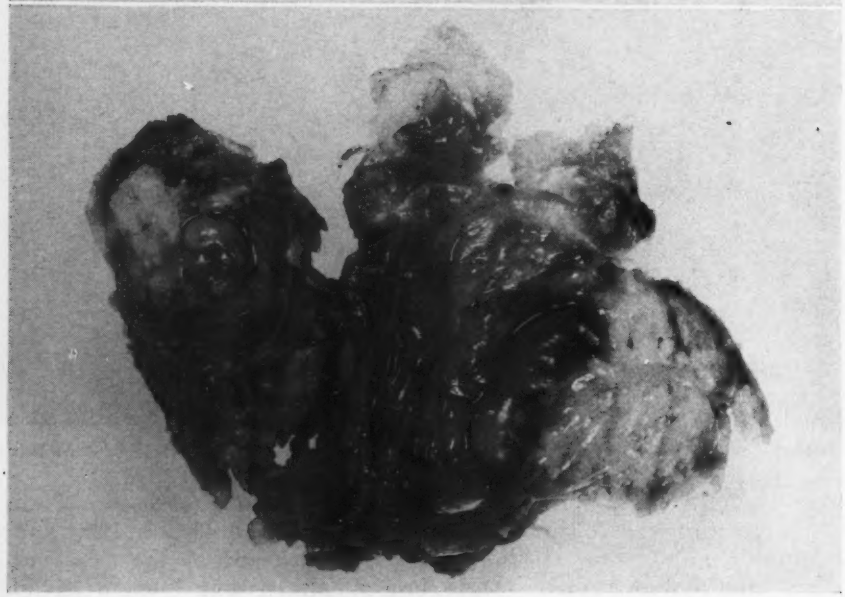

Fig. 7.—Twin abortuses (in intact specimens) before the opening of the sacs. (×1½; reduced ¼.)

Fig. 8.—Same as Fig. 7 after the sacs were opened, disclosing stunted fetuses. (×1½; reduced ¼.)

quent histologic findings may demonstrate molar change particularly in those fetuses that show a greater degree of abnormality. Six of 9 specimens demonstrated molar change in cases where a fetus was not present. In the instances of a nodular fetus which we consider the next degree of abnormality,

6 showed molar change and 2 showed questionable molar change. Of 16 specimens of the cylindrical fetuses examined molar change was demonstrated in 10. Of 22 specimens with stunted fetuses, 9 showed molar change. In those

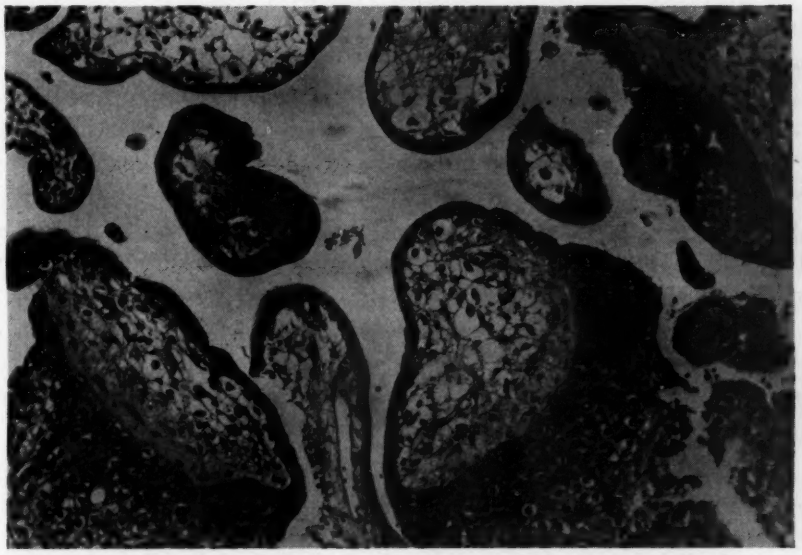

Fig. 9.—Anchoring villi from a normal placenta. (×100; reduced ¼.)

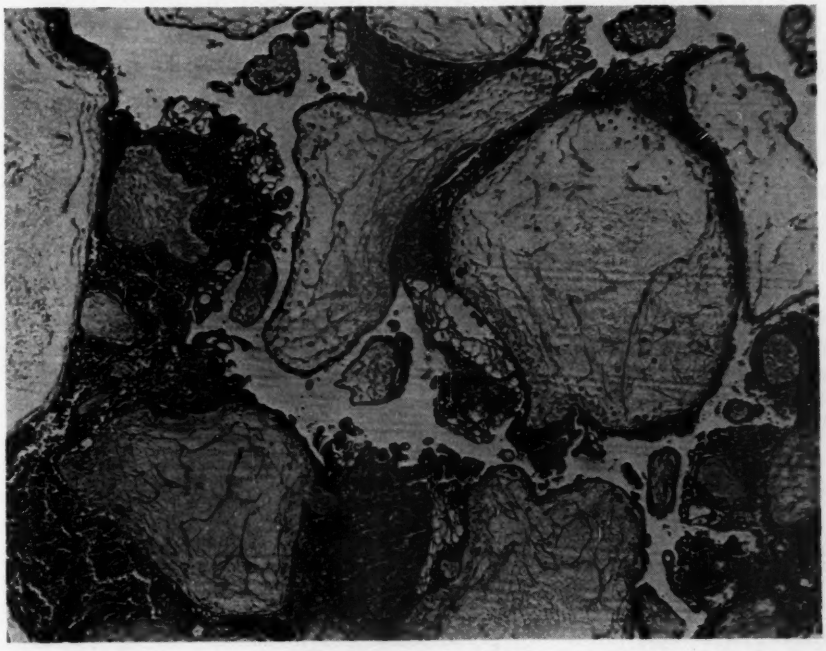

Fig. 10.—Transitional mole. (×100; reduced ⅕.)

with macerated fetuses, which is the least degree of abnormality, molar change was demonstrated in 3 of 9 specimens examined. Proliferation of trophoblastic cells is the surest of the criteria to evaluate. One should be cautious to avoid interpreting anchoring villi as evidence of trophoblastic proliferation (Fig. 9).

We consider one specimen intermediate between molar change of the placenta and true hydatidiform mole and we choose to classify it as a transitional mole.[3] In this specimen the fetus was stunted for the sixteen weeks' calculated gestation and small vesicular villi were noted without the aid of the dissecting microscope. Fig. 10 demonstrates the obvious molar change with occasional markedly enlarged villi.

It is interesting that of the 90 complete specimens examined, normal fetuses were found in only 22 instances (24 per cent). In none of these was molar change present. The remaining 68 (76 per cent) were abnormal. In these 68 specimens molar change was diagnosed in 36. This represents 53 per cent of the pathologic fetuses or 40 per cent of the total group. It is also to be noted that the average duration of pregnancy was 11.6 weeks in instances showing molar change and 13.3 weeks in those in which it was not demonstrated.

In this series, when molar change was demonstrated, an abnormal fetus was present. When molar change was not demonstrated (54 of 90 specimens), the fetus was abnormal in 32 instances.

If one is justified in drawing conclusions from this group of abortion specimens, then clinically he would consider that more than half of the patients who abort have an abnormal conceptus. If it were possible to prevent the abortion in this group 40 per cent of whom showed molar change, then the frequency of the development of hydatidiform mole would be many times increased. The data obtained in this study confirm in general the findings reported by Hertig and Edmonds, and may be summarized as follows:

1. Of the 90 intact specimens obtained from the material of 314 abortions an abnormal fetus was demonstrated in 68 (76 per cent).

2. In 40 per cent of all the intact specimens changes were demonstrated in the chorionic tissue which were characteristic of beginning hydatidiform mole. These changes in our series were always associated with an abnormal fetus.

We are indebted to Drs. Paul Evans and John Shively of the Pathology Department of Indianapolis General Hospital for their aid in the collection of the specimens. Drs. Thomas A. Stump and Joe Atlas aided considerably in the preparation of specimens. Messrs. James F. Glore, Paris Johnson, and Robert Albright aided in the preparation of the illustrations.

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Discussion

DR. J. P. GREENHILL, Chicago, Ill.—In the past little clinical significance has been attached to molar changes in abortion specimens. The only worth-while articles on this subject have been those by Mall and Meyer published 35 years ago, and by Hertig and Edmunds, which appeared 9 years ago. The authors of both of these papers also pointed out that most obstetricians consider molar degeneration to be rare in spite of the fact that it is common.

The chief reason for this erroneous belief is that most of the conceptuses which are expelled spontaneously are either discarded without examination or studied only perfunctorily with a mental "shrug of the shoulders" as not being worthy of serious attention. It is a rare pathologist who is interested in spending the necessary time required properly to examine abnormal ova even if he knows enough about early embryos and the pathology of the placenta.

Huber and his associates state that molar changes were not demonstrated in their 3 cases of missed abortion. In a case of missed abortion which had been retained in the uterus for 20 weeks after development had ceased, I found in a case reported in 1921 that many of the villi showed some edema, but what was very conspicious was the almost entire absence of blood vessels or the remains of blood vessels in the villi. The latter finding is Huber's first histologic criterion of molar change and edema is the second criterion. Hertig and Edmunds pointed out that a hydatidiform mole constitutes a type of "missed abortion."

Huber and his associates agree with Hertig and Edmunds that about half the patients who abort have an abnormal conceptus. How can this fact be reconciled with the claims of some obstetricians who maintain that they observe live babies in 95 per cent of cases of threatened abortion treated by hormones, vitamins, thyroid, bed rest, and other measures?

In at least half the cases of threatened abortion something appears to go wrong with the conceptus before the bleeding and cramps occur. These signs indicate that an effort is being made by the uterus to expel an abnormal product of conception. If the conceptus is abnormal, medication will seldom succeed in preventing its expulsion. If treatment stops the bleeding and contractions, it can lead to an increased number of hydatidiform moles, as Huber and his associates say. Perhaps some day we shall have therapy which will prevent the abnormal changes which occur in the first few weeks (not months) of pregnancy. In the meanwhile, may I make a plea that *all* abortuses be examined carefully by individuals who have special training for this? Few hospitals have such interested and trained pathologists. Hence I urge that *all* conceptuses be sent to laboratories where such specimens will be properly investigated. For many years the Carnegie Laboratory of Embryology in Baltimore has been the recipient of a large number of normal and abnormal conceptuses. Now that Huber and his associates are interested in this important subject, let us avalanche them with such specimens.

DR. JOHN E. SAVAGE, Baltimore, Md.—According to Kossman, Hippocrates ascribed the "grape-mole" to mucoid degeneration of the villi. Aëtius of Amida, in the sixth century, also described this condition. Giffard, in 1734, reported what appears to be the first recorded case of hydatidiform mole in England. Early in the nineteenth century, Madame Boivin, one of the most famous of the Paris midwives, was among the first to write intelligently about hydatidiform mole, and is credited with pointing out that the vesicles are the product of a disease of the chorion. Both Velpeau and Meckel wrote of this entity and Virchow revived the Hippocratic theory as to its etiology. The writings of Marchand and Frankel, late in the nineteenth century, form the basis of the modern literature on this subject.

Concerning the history of molar changes in the chorionic tissue of aborted ova, DeLee, in the first edition of his text, in 1913, stated that he had frequently found evidence of degenerated villi with vesicle formation. Meyer stated that mole formation probably is the commonest of all diseases of the ovum during the earlier months of gestation, and suggested that the typical large hydatidiform mole is the end result. Mall and Meyer, in 1921, called attention to the frequency of hydatidiform degeneration in early abortions, especially those in which an abnormal fetus was found. Hertig and Edmonds, in 1940, in an exhaustive study of 1,027 spontaneously aborted ova, reported hydatidiform degeneration in 40 per cent. The results of the present contributors generally agree with those of Hertig and Edmonds.

If more specimens from patients with repeated abortion and missed abortion had been available for study, one wonders if molar change in the chorionic tissue would have been shown to be a significant etiological factor.

Because of the correlation of the high incidence of molar change in the presence of a pathologic fetus, could this phenomenon, in lesser degree, have teratologic implications?

We would be interested to know whether or not the authors have made hormone assays either in their routine study or in their continuation observations.

DR. MELIN.—From the study we thought that in classifying these specimens as to whether they demonstrated molar change we had arrived at useful criteria. The illustration of a twin abortus was very interesting to us, and we subsequently detected four additional twin abortuses. Two of the specimens of twin abortuses demonstrated molar change. We had one patient who was a habitual aborter, and the specimen rather conclusively demonstrated the absence of a fetus and molar change of the chorionic villi. I might add that we look forward to examining specimens from habitual aborters in the future.

The only additional comment that I should like to make is that, of the specimens where molar change was demonstrated, the average gestation was 11.6 weeks, and in those specimens where molar change was not demonstrated the period of gestation was 13.3 weeks.

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—The frequency with which this hydatidiform-like change in the chorionic tissue has been noted in spontaneous abortions is amazing and may lead us eventually to alter our concept of the frequency of molar conditions.

One wonders whether there is a direct or progressive relationship between these hydatidiform-like alterations in the chorion and the fully developed and characteristically structured hydatidiform mole. One may accept the thesis that hydatidiform mole in its fully developed and characteristic form inevitably causes death of the embryo and usually its absorption. On the other hand it appears quite possible that early and primary death of the embryo might be associated with subsequent appearances in the chorionic epithelium which would suggest a hydatidiform mole. The primary death of the embryo might indeed be followed by collapse of the feebly developed circulatory system in the stroma of the villus, and the appearance of some edema of the villus stroma. Even proliferation of the chorionic epithelium might be expected to continue for some little time after primary death of the embryo, inasmuch as the chorionic epithelium is nourished by maternal blood and not by fetal.

It must be recognized, however, that this early hydatidiform-like change may actually be related to the peculiar biologic relation between maternal resistance and the naturally invasive property of chorionic epithelium, representing a chain of lesions from the mildest type of development with death of the embryo to the most serious forms of choriocarcinoma.

DR. HUBER (Closing).—Dr. Savage raised the question of whether hormone studies were done. I am sorry to have to report that these were not done, although they would certainly give very interesting additional information.

In missed abortion, we did not find molar change. It is our belief that perhaps the conceptus in these cases had been expelled before molar change had time to develop.

The questions which Dr. Montgomery raised I think are very important ones. Certainly it is impossible to prove that there is any inevitable relationship between these changes and the development of the clinically recognized hydatid mole. On the other hand, I think it is quite evident that the changes that take place seem to be progressive. The increase in the degree of this change and the number of villi that show this sort of a change seem to be correlated with the length of time that has elapsed before the conceptus was expelled.

UTERINE CONTRACTILITY, CIRCULATION, AND URINARY STEROIDS IN PREMATURE DELIVERY*†

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IN A previous report[6] urinary estrogen-pregnanediol levels were correlated with uterine motility during normal full-term pregnancy. In the present study, further observations were made on uterine contractility and urinary steroid metabolites in patients who were delivered prematurely. In addition, uterine circulation measurements, by the use of an isotope technique, were employed to investigate the mechanism of premature delivery. This study represents an attempt to correlate various changes in uterine physiopathology which occur in patients who are delivered prematurely.

Material

A total of 58 pregnant women are included in the study. They are divided into the following four groups: 16 patients had normal uncomplicated pregnancies and were delivered at term; 16 patients were delivered prematurely and were compared to the 16 normal patients; 10 women were selected because of a poor obstetrical history of repeated premature deliveries or habitual abortions. Five of the latter were given estrogens and 5 were used as controls. Uterine circulation studies were done on another group of 16 pregnant women near their delivery dates. Eight of these had normal full-term pregnancies and 8 had premature deliveries.

Methods of Study

Selection of patients, assay of urinary estrogens and pregnanediol, and recordings of uterine motility were described in detail in previous communications.[1, 6] Ten patients with poor obstetrical histories were selected for special study at the thirtieth week of pregnancy. Five of the latter were given 60 mg. of natural estrogens‡ per day for two weeks. Measurements of urinary steroids and uterine motility were done before, during, and after administration of the drug. The natural estrogens were given to these patients at the thirtieth week of pregnancy to study its specific effect upon measurable uterine contractility and excretion of urinary estrogens and pregnanediol. Estrogens were not given as a therapeutic agent to prevent premature delivery.

Measurement of effective uterine circulation was patterned after that of Kety[3] and Morris and associates[5] with the following modifications. Five microcuries of $Na^{22}Cl$ were diluted to 0.2 c.c. with isotonic saline, sterilized, and injected into the uterine muscle. The site for the injection was 2 inches below

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‡Premarin, 15 mg. capsules, supplied by Ayerst Laboratories, New York, N. Y.

and 2 inches to the left of the umbilicus. The counting rates were made with an end-window Geiger tube attached to a ratemeter. Readings were made at intervals of 15 seconds, continued until the originally injected isotope had largely disappeared from the uterine muscle. The results obtained were plotted on semilogarithmic graph paper, after the counting rate had been corrected by the formula published by Morris.[5] These results were expressed as time to half-value in minutes which is the time for one-half of the injected radioactivity to disappear from the uterine tissue.

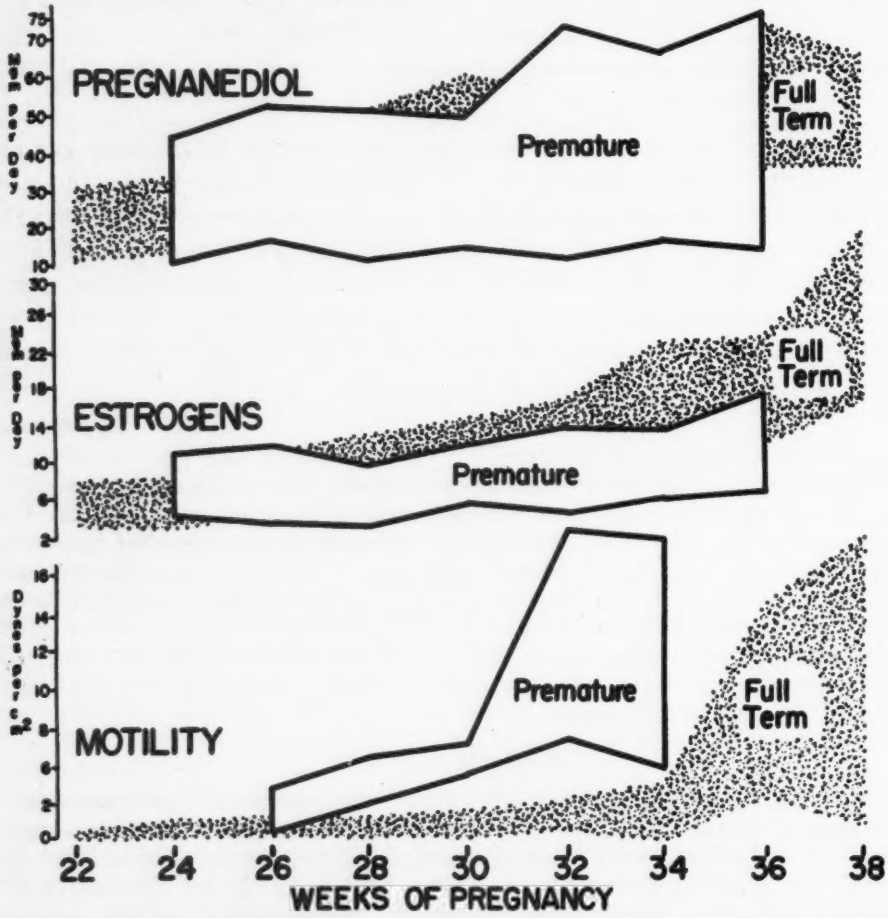

Fig. 1.—Correlation of steroids and motility. The dotted backgrounds are 16 normal full-term deliveries. The boxed-in areas represent a total of 16 premature deliveries from all causes. Urinary pregnanediol and estrogen trends in premature delivery are, in general, low and show less tendency to rise as pregnancy progresses. Uterine motility is excessive throughout the latter portion of pregnancy regardless of the levels of urinary steroid metabolites.

Results

A. Urinary Estrogen-Pregnanediol Levels and Uterine Contractility in Premature Delivery.—

A total of 16 patients were delivered prematurely. Five of these had been previously reported upon[6] and are included in this study. Four patients, for reasons unknown, were delivered spontaneously. Labor was induced prematurely in 3 for obstetrical indications. Two had premature rupture of the membranes, 2 pyelonephritis, 2 toxemia, one adenomyosis, one procidentia, and one had fibroids. A summary of their clinical and laboratory data is presented in Table I and Fig. 1.

The 16 patients who were delivered prematurely showed low urinary estrogen excretion and excessive uterine contractility when compared to the 16 normal patients. Those who were delivered spontaneously and prematurely had the same low levels of estrogens and excessive uterine activity as patients in whom labor was induced for obstetrical indications. In severe pre-eclampsia, urinary estrogens were low regardless of whether or not the pregnancy was interrupted.

TABLE I. CLINICAL AND LABORATORY DATA

Summary of Data on 16 Premature Deliveries

CASE	AGE		PARITY	COMPLICATION	WEEKS' GESTATION	WEIGHT OF INFANT (GRAMS)
57*	20	White	0	Spontaneous delivery—none	36	2,420
71*	16	Sp. Am.	ii	Spontaneous delivery—none	35	2,200
73*	33	White	ix	Spontaneous delivery—none	35	2,180
D	21	Negro	iii	Spontaneous delivery—none	36	2,180
28	33	White	v	Induced labor—diabetes	37	2,250
80*	22	White	v	Induced labor—toxemia	36	2,230
G	21	White	0	Induced labor—toxemia	35	1,868
B	24	Sp. Am.	iii	Premature rupture of membranes	35	2,300
S	33	Negro	iv	Premature rupture of membranes	38	2,350
F	35	Sp. Am.	v	Pyelonephritis	40	2,370
N	33	White	iv	Pyelonephritis	31	1,500
C	29	Indian	viii	Toxemia	40	1,868
K	19	White	0	Toxemia	34	2,220
19*	35	White	iv	Adenomyosis	36	2,400
84	31	Negro	iii	Procidentia	34	1,500
Y	23	Negro	iii	Fibroids	26	1,150

Uterine Contractility

WEEKS' GESTATION	NO. DETERMINATIONS	% PATIENTS WITH ACTIVITY	UTERINE WORK (DYNES/CM.²)		
			AVERAGE	50 PERCENTILE	75 PERCENTILE
26	11	55	5.7	0.1	1.8
28	12	67	7.8	1.4	3.5
30	13	62	13.3	3.1	4.2
32	10	80	12.2	5.0	18.4
34	11	82	10.2	3.7	18.1

Urinary Pregnanediol and Estrogens

WEEKS' GESTATION	NO. DETERMINATIONS	PREGNANEDIOL (MG./DAY)		ESTROGEN (MG./DAY)	
		MEAN	S.D.	MEAN	S.D.
24	7	29.9	14.0	6.3	2.5
26	12	35.3	17.7	6.2	3.3
28	11	32.0	19.2	4.7	2.4
30	14	32.9	17.7	7.5	2.3
32	11	41.3	29.8	8.2	3.7
34	11	40.4	24.6	8.0	3.3
36	5	45.8	34.1	10.7	5.5

*These patients were reported upon previously.[6]

In these studies, only low estrogens and not low pregnanediol were associated with excessive contractility. Some patients, however, notably those with severe toxemia, showed low levels of both steroid metabolites. Patients who were delivered prematurely and whose only associated obstetrical complication was premature rupture of the membranes had excessive uterine contractility before the defect in urinary estrogens and pregnanediol became evident. An excessive uterine motility was also prominent in patients with severe pyelonephritis and adenomyosis uteri.

B. Urinary Estrogen-Pregnanediol Levels and Uterine Contractility in Patients With Histories of Repeated Premature Deliveries or Habitual Abortion.—All 10 patients with poor obstetrical histories exhibited an excessive amount of uterine activity when compared to normal patients. Five who were given oral estrogen had no diminution of uterine contractility during the thirty-second week of pregnancy while on estrogen therapy (Fig. 2). Although urinary estrogens were elevated after oral estrogens were given, partitioning of the total urinary estrogen metabolites showed that estriol, the endogenous estrogen metabolite, was not increased. The augmented urinary estrogen was due to estrone from the administered estrogen. Natural estrogens, given for two weeks, did not suppress the excessive uterine contractility which usually characterized the obstetrical patient who had lost several previous pregnancies prematurely. Although the results of this preliminary study are of clinical interest, no statistical significance can be attributed to the measurements because of the small number of determinations.

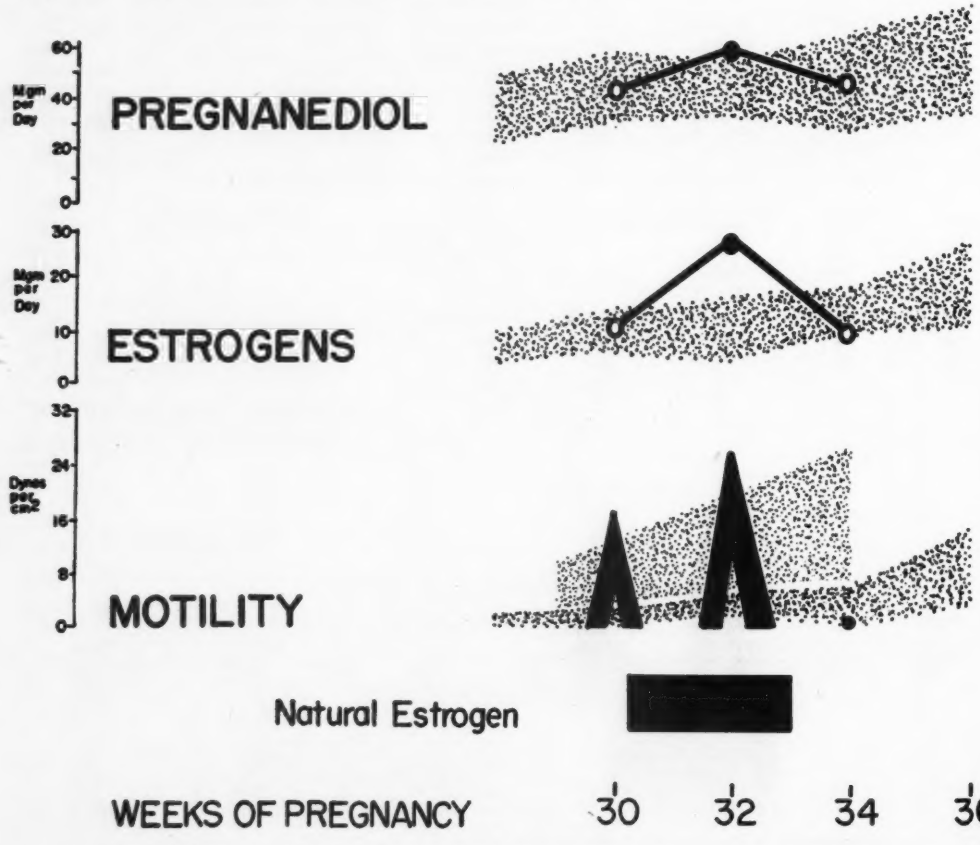

Fig. 2.—Estrogen administration. Natural estrogens (60 mg. per day for 2 weeks) were given to 5 patients with poor obstetrical histories and determinations were made at the thirty-second week. The thirtieth and thirty-fourth weeks were used as controls. Urinary pregnanediol values were unchanged. Urinary estrogens were elevated. Excessive uterine motility was unsuppressed while the patients were on natural estrogens.

C. Effective Uterine Circulation in Premature Delivery.—

The radioactive $Na^{22}Cl$ was injected into the uterine muscle of 16 pregnant patients (Table II). Six were normal multiparas near term, not in labor, and 2 were normal primiparas. The average time for half of the radioactivity to

disappear from the uterine muscle was 4.2 minutes ±0.9. This time was comparable to the average figure of 4.1 minutes ±0.4 obtained from 20 normal patients by Morris.[5] In 8 patients who were delivered prematurely, the comparable average time for half the radioactivity to disappear was 7.3 minutes ±2.9. Premature delivery in this group of eight patients was associated with a diminished clearance rate of $Na^{22}Cl$ from uterine tissue (Fig. 3). The test of the significance of difference between means is highly significant. P equals 0.02 to 0.01. Hence, effective uterine circulation is reduced in women who are delivered prematurely regardless of the presence or absence of a discernible disease and the degree of circulatory reduction appears to be related to the severity of the maternal or obstetrical complication.

TABLE II. SUMMARY OF DATA ON UTERINE CIRCULATION STUDY

PATIENT	AGE	PARITY	COMPLICATION	WEEKS' GESTATION	WEIGHT OF INFANT (GRAMS)	T/2 HOURS	T/2 MIN.
Full-Term Delivery.—							
O. W.	17	0	None	37	2,690	5	0
E. A.	27	iv	None	38	2,800	2	30
F. K.	27	0	None	39	2,600	5	0
A. G.	31	vi	None	40	2,730	4	30
D. B.	26	i	None	40	3,100	5	15
A. R.	21	ii	None	40	3,630	3	30
D. V.	20	ii	None	41	3,600	4	15
S. M.	22	iv	None	38	3,840	3	15
Premature Delivery.—							
G. P.	30	iii	Spontaneous delivery—none	40	2,400	4	30
G. C.	29	iv	Spontaneous delivery—none	35	2,370	7	45
J. K.	21	iii	Spontaneous delivery—none	35	2,020	7	30
A. V.	21	i	Mild toxemia	38	2,400	4	15
M. A.	22	ii	Mild toxemia	37	2,500	5	30
G. V.	21	ii	Mild toxemia	35	2,250	5	15
B. G.	32	iii	Separation	34	2,200	12	15
J. M.	22	i	Abruptio placentae	31	1,920	11	45

Comment

This study was originally designed to correlate urinary steroid metabolites with uterine motility in normal and abnormal pregnancies. As the project evolved, it became apparent that low urinary estrogen levels and excessive uterine motility bore some relationship to premature delivery. It was reasoned that estrogen replacement therapy might alter the hypermotility and low steroid patterns either by a direct action on uterine muscle or indirectly by increasing uterine circulation. However, when supplementary estrogens were given to a select group of patients, no significant change in uterine motility occurred. It was noted, nevertheless, that a reduced uterine circulation was characteristic of patients who were delivered prematurely regardless of whether or not they received estrogen therapy. The question then arose as to whether the two defects, excessive uterine contractility and low urinary steroids, were both related to a reduction in uterine circulation. An important lead in this direction was afforded by the data obtained from 6 patients, not included in this

study, who had urinary estrogen and pregnanediol determinations, uterine contractility measurements, and uterine circulation rates done simultaneously. Three of these patients were delivered of premature infants near the thirty-sixth week of gestation. Two of the latter showed low urinary steroid metabolites, excessive uterine motility, and reduced uterine circulation. Of the other 3 patients who were delivered of full-term infants, 2 showed normal values for the correlated contractility, circulation, and steroid studies. These trends again suggest that reduced uterine circulation in prematurity may give rise to the observed defects in uterine contractility and urinary steroids.

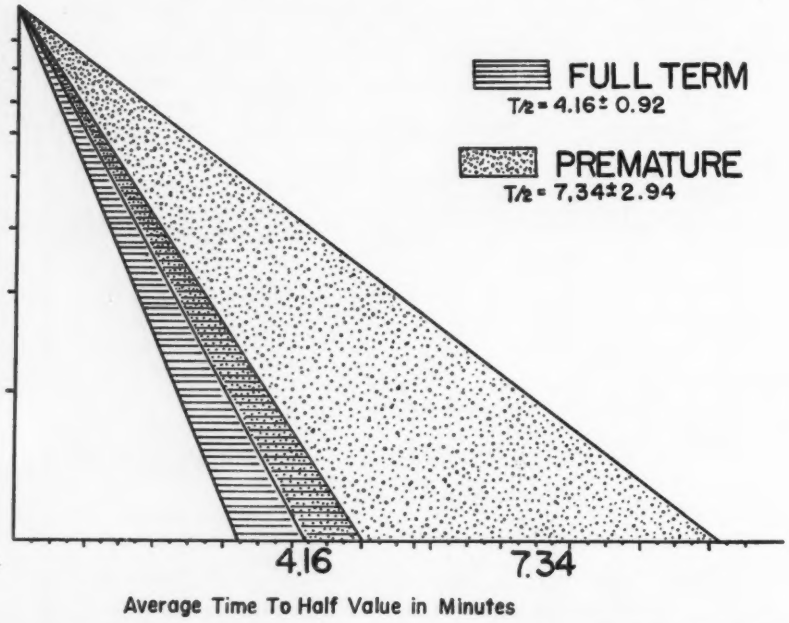

Fig. 3.—Effective uterine circulation. Clearance rates of $Na^{22}Cl$ from uterine muscle in 16 patients. The initial counting rate has been equalized so that the results appear as arbitrary counting units plotted against the time required for one-half of the radioactivity to disappear. The lined area represents 8 normal full-term deliveries, showing an average time to half-value of 4.2 minutes. The dotted area represents 8 patients who were delivered prematurely. The average time to half-value was 7.3 minutes, almost twice the normal value.

If the underlying physiopathology of premature labor is uterine circulatory insufficiency, then diverse maternal disease and obstetrical complications which are often associated with prematurity[7] become understandable. For example, in essential hypertension, uterine vascular insufficiency may be one aspect of a generalized chronic disease process. In eclamptogenic toxemia, the locally reduced uterine circulation may be only a part of systemic vasospasm. In both of these disease processes, the severe forms frequently give rise to small infants and small placentas regardless of the length of gestation. Therefore, a prolonged reduction in uterine circulation may be responsible for both the small fetus and the small placenta. It is possible also that subclinical toxemia, especially in primiparas, may be diagnosed as spontaneous premature labor, cause undetermined.

Local uterine diseases such as diffuse adenomyosis, multiple fibroids, congenital anomalies, and prolapsus also may be associated with a reduction in uterine circulation. Two patients in this study displayed abnormal bleeding tendencies during pregnancy and showed diminished levels of urinary estrogens and pregnanediol. Both of these patients had vaginal hysterectomies done several months following premature delivery. Pathological examination of the specimens showed uterine hypertrophy, endometrial hyperplasia, adenomyosis, leiomyomas and carcinoma in situ. These findings also support the thesis that many of the accidents of pregnancy which terminate in premature delivery are part of an underlying endocrine-vascular disorder.

Theobald[8] points out that arteriolar constriction, however it is effected, can almost invariably be abolished by vasodilator drugs. Morris[5] has demonstrated an increase in effective uterine circulation in 5 patients with severe pre-eclampsia after therapy with hypotensive drugs. When it is realized that any degree of pregnancy toxemia, especially in conjunction with primigravidity, multiple pregnancy, and hypertensive disease, accounts for a large segment of premature deliveries, then the use of drugs to restore a deficient uterine circulation to normal might contribute immeasurably toward the prevention of prematurity. In any event, the mechanism and time of onset of reduced uterine circulation in patients who are delivered prematurely for any reason need further exploration.

The association of premature delivery with reduced uterine circulation is also of interest in a complication of the newborn called the pulmonary hyaline membrane syndrome. Miller and others[2, 4] have suggested that this process begins in utero secondary to anoxia. The findings in this study might explain how complicated or uncomplicated premature labor could give rise to fetal hypoxia, resulting in hyaline membrane disease.

Conclusions

1. In this study the onset of premature labor was frequently accompanied by maternal disease and obstetrical complications.

2. Premature labor, from whatever cause, was usually associated with an excessive uterine contractility and reduced excretion of urinary estrogens.

3. Effective uterine circulation was reduced in women who were delivered prematurely, regardless of the presence or absence of an overt disease.

4. The degree of uterine circulatory reduction appears to be related to the severity of the maternal or obstetrical abnormality.

5. Low urinary estrogen levels and excessive uterine activity in patients who are delivered prematurely probably are not related as cause and effect, but are manifestations of another aberration, probably reduced uterine circulation.

6. In patients who had previous premature deliveries or habitual abortions, natural estrogens given for a two-week period did not suppress excessive uterine contractility.

We wish to thank Drs. J. Aikawa, J. Dodge, C. McIntyre, and E. Weis, Jr., for their technical and clinical assistance in this study.

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Discussion

DR. ROBERT B. WILSON, Rochester, Minn.—Dr. Bruns and his associates have shown us in this report that premature labor is preceded by increased uterine irritability, reduced urinary excretion of estrogen and pregnandiol, and reduced uterine circulation as determined by the disappearance of labeled sodium chloride.

With these findings it is immediately apparent that the fetal oxygen supply is reduced and that fetal hypoxia must be present. As Eastman has so often said, hypoxia remains the greatest threat the fetus in utero has to face. It is for this primary reason that this is such an important and worth-while study, for it reveals that in many ways the state of uterine blood flow and uterine irritability is the same in patients who experience premature labor as in those who have toxemia or who experience some other serious obstetric complication and in whom the fetal salvage is often so poor.

Dr. Bruns and his colleagues have searched for a reason for this decreased uterine blood flow and increased uterine irritability in certain abnormal states and have directed their search toward abnormal estrogen and progesterone metabolism. While their studies did disclose evidence of endocrine abnormalities they were unable to resolve the problem by the administration of an estrogen complex.

One criticism which might be made of this work, and it may not be a valid one, is that in this phase of the study estrogens were administered for but two weeks and estrogen and pregnandiol assays and uterine-motility studies were made only one time during the administration of the estrogens. Furthermore, the authors do not report any Na^{22} studies in relation to the administration of the estrogens. As we all know so well, it is most difficult or almost impossible to correct an abnormal endocrine situation during pregnancy once it has developed. It appears, therefore, that before an endocrine basis can be excluded, treatment with estrogens and perhaps other hormones should be started earlier and given longer to properly selected patients and that the experimental studies should be done at reasonable intervals during the time the hormones are administered.

It also seems that chorionic gonadotropin should be studied as well as the adrenal steroids, and even perhaps relaxin, before an endocrine factor is excluded.

The authors surmise that ineffective uterine circulation may be the common denominator in many obstetric difficulties. It does not seem to be that simple, however, for we are faced with the age-old question of which is the cause and which is the effect. Is the uterine irritability, shall we say, the cause of the decreased circulation or does the decreased circulation cause uterine irritability and in due time premature labor? Are the decreased circulation and increased uterine irritability due to a generalized or local maternal vascular abnormality or are all of these things due to some physiologic or anatomic abnormality of the pregnancy itself? Furthermore, it is rather remarkable that there were no patients with increased uterine irritability and decreased circulation who had normal pregnancies which went to term without evidencing a serious obstetric complication. It seems pertinent to inquire whether or not this is universally the situation.

Since the theory of a reduced uterine circulation or uterine ischemia is the most common present-day theory as to the cause of toxemia, I would like to ask if the authors

feel that these patients who had increased uterine irritability and decreased uterine circulation might have developed a toxemic process had nature not so fortuitously interrupted their pregnancies prematurely?

Last, the use of the word "clearance" to describe the disappearance of labeled sodium chloride seems unwise and confusing, as, in this situation, with the procedure described in the report, the authors have measured only the rate of disappearance of a labeled substance. Some also might question the validity of assuming that the disappearance of labeled sodium chloride is a reasonably accurate measure of uterine circulation. The fact that sodium chloride is retained by the pregnant female during the latter months of pregnancy is well known. It may be that in these patients a diminished rate of disappearance of labeled sodium chloride may reflect an abnormal retention of salt rather than indicate decreased circulation.

DR. D. E. CANNELL, Toronto, Ontario.—Dr. Bruns' patients were selected for study after the twentieth week of pregnancy. In Toronto, Robson and Gornall (Canadian Medical Association Journal 72: 830, 1955) found that decreased pregnanediol excretion was almost invariably associated with subsequent abortion. Premature labor and abortion have features in common, though with a difference in timing, which may account for the apparent discrepancy in results reported by these two groups of investigators.

The therapeutic significance of Dr. Bruns' work is not easy to determine. He suggests that the increased uterine motility and decreased excretion of urinary steroid metabolites may be manifestations of a primary impairment in uterine circulation. If this be so, Morris' finding of improved uterine circulation in pre-eclampsia, where hypotensive drugs were employed, may be of value in the prevention of premature labor in this condition. Is Dr. Bruns aware of any evidence that this has been proved to be true?

No matter what therapeutic value becomes evident from this project, Dr. Bruns and his colleagues are to be commended for their painstaking work and the reserve with which they have drawn conclusions from their results.

DR. FREDERICK FALLS, Oak Park, Ill.—Dr. Bruns has indicated that in these patients with premature labor he can demonstrate circulatory changes. I'd like simply to correlate his ideas with some of my own on the subject of abortion.

The irritability of the uterus may be controlled by hormone treatment, but why is it necessary to increase progesterone in the blood of a woman who has a tendency to habitual abortion or premature labor? For a good many years we have been interested in the configuration of the uterus in women who have a history of habitual abortion, and we find on investigation that a rather large percentage of these women show evidence of an abnormality in the contour of the uterus. We believe that many of them have bicornate uteri of the arcuate type, and as a result these uteri are not physiological in the sense that they cannot retain a conceptus as well as the uterus that is not so deformed. It is also possible that if they show gross anatomical change, such as a distinct notch in the fundus at term or a marked deviation to one side, there may be significant changes in the innervation and circulation and as a result abnormal formation of decidua and placentation. So from the very start of pregnancy conditions surrounding the developing embryo are abnormal. These facts might easily be correlated with Dr. Bruns' observations.

DR. LOUIS M. HELLMAN, Brooklyn, N. Y.—Dr. Bruns was careful at the beginning of his talk to say that he was not measuring the flow in talking about circulation, and yet at the end he resorted entirely to a discussion of uterine blood flow. I believe it is well to pause and consider exactly what was measured.

There have been numerous attempts, particularly in the past three or four years, to measure uterine blood flow in experimental animals where the abdomen could be opened and substances could be injected into the circulation and attempts made to determine the flow. Most of this work has been done by Dr. Barron and the group at the Boston Lying-in Hospital. Today I am sure these investigators would hesitate to say that even

in these experimental animals they have accurately measured the uterine blood flow. So far as I know, the only real attempts to do this in the human being have been done by this group and by Assali in Los Angeles. Neither of these groups of investigators has anything more than approximation of the uterine blood flow.

Dr. Brown and James Walker have also attempted to measure the flow by injecting sodium into the uterus, both into the muscle as Dr. Bruns indicated, and into the intervillous space. Neither of these investigators has made much claim that he has measured uterine blood flow, nor do I think they have. So it is quite conceivable that what one is measuring is speed of exit of blood from the uterus and not flow. There is, according to Brown and Walker's work, a very marked difference in the sodium disappearance when injected into the muscle and when injected into the intervillous space. I do not think one can draw the conclusion that just because sodium disappears more slowly from the muscle in the abnormal cases that one has established anything concerning the circulation in the intervillous space which is all important to the fetus and its growth.

Finally, a word about oxygen. I do not think that one can say that because circulation is diminished this necessarily means the fetus is short of oxygen. There are two factors which control the amount of oxygen that goes to the fetus. The most important is the gradient across the placenta of the partial pressure of oxygen on the mother's side and the partial pressure of oxygen on the fetus' side. The second factor is the flow. While it is at least theoretically possible that the flow through the intervillous space can be so fast that the fetus is deprived of oxygen, it is just as possible that it can be too slow. So, without criticism of anything that Dr. Bruns has said except his use of the word "flow," I would just like to raise these points as elements of caution.

DR. E. C. HUGHES, Syracuse, N. Y.—Several years ago we reported the pregnanediol excretion in normal and premature pregnancies. We included in that presentation the excretion of chorionic gonadotrophin throughout the entire length of gestation.

I had hoped that in the present paper the pregnancy could have been studied earlier so that the amount of gonadotrophin excretion could also be studied.

We found in the premature pregnancy that the amount of chorionic gonadotrophin which was excreted in early portions of the pregnancy was far under the normal amount, and that the peak of excretion was not reached at the normal time of gestation, which was approximately 50 days. The peak excretion of chorionic gonadotrophin was as late as 80 to 90 days in the patients who delivered a premature fetus. Therefore, it seems to us that the primary disease in this condition is one found in the placenta early in pregnancy.

Studies of the placenta in these premature patients have shown findings similar to those which Dr. Huber has described this morning. In other words, there was avascularity of the placenta, edema of the villi. There was also a recurrence of some of the cells of the chorion which were present in the early portion of gestation, which normally disappear as the pregnancy advances.

We found in the normal patients, with tissue obtained at therapeutic abortion, that about 10 per cent of the villi were hydropic. I think if we search deeper into those specimens we will find this pathological or physiopathological state.

I do not feel that the administration of any of the steroids during pregnancy will prevent prematurity, but the development of a good endometrium and decidua before conception and implantation of the fertilized ovum take place may be the answer.

TRANSFER OF D- AND L-HISTIDINE ACROSS THE HUMAN PLACENTA* †

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THE increased concentration of amino acids in fetal as compared to maternal plasma was recorded as early as 1914,[1] and the observation has been confirmed several times.[2-10] Christensen and Streicher[7] found that the fetal to maternal amino acid ratio varied from 5:1 in the guinea pig to 1.7:1 for the human species. They concluded that the placenta must act as a "pump" in order to maintain such a concentration gradient. Until 1950 these calculations were based upon measurements of total free alpha-amino nitrogen but in that year Crumpler, Dent, and Lindan,[8] using chromatographic methods, demonstrated that each individual essential amino acid was higher on the fetal side.

That it is the trophoblastic epithelium rather than the fetus which is responsible for this "concentration" is indicated by the findings of McKay and associates,[11] who measured the total amino acid concentration of hydatid mole fluid and found it to be twice that of the maternal plasma.

Such findings are consistent with the hypothesis that there is an active transport mechanism for amino acids across the placenta, but the demonstration of such a mechanism has not, to our knowledge, been recorded. Amino acids are relatively small molecules and they should be able to traverse most living membranes by simple diffusion. If there also are present in the placenta biochemical systems for active transport of these important materials (and such systems do exist in the epithelia of the renal tubules and the intestine) it might be assumed that such processes would be highly selective. The placental barrier might possess a carrier system for the naturally occurring amino acids but not for the unnatural isomers. It is inconceivable that rates of diffusion could differ for any given pair of optical isomers; so the demonstration of a more rapid transport for the natural L- configuration as opposed to the D- form should be proof of active transfer. The experiments described below were designed to test this hypothesis. DL-histidine was selected for study because of our familiarity with the metabolism of this amino acid in pregnancy and because of the availability of reliable methods for determining total as well as L-histidine in plasma.[12-15]

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Methods

Eleven healthy pregnant women at or near term were selected for study, the only basis for selection being the predictability of the time of delivery. For this reason, 9 of the subjects were chosen because they were scheduled for elective repeat cesarean sections under local or spinal anesthesia.

At intervals which varied from 9 minutes to 4 hours before delivery, a priming dose of 500 mg. each of L- and D-histidine was given to the mother intravenously. This was followed by an infusion of 5 per cent dextrose in water containing enough of the histidine so that a rate of 4 ml. per minute delivered from 10 to 12 mg. of each isomer per minute. It was found advantageous in the later experiments to administer the L- form at a rate slightly faster than the D- form in order to maintain constant blood concentrations of each.

Maternal blood samples were taken before the priming dose and several times thereafter, the final sample being collected within 2 minutes after delivery of the baby. Venous cord blood was collected within 30 seconds after delivery. In one case (L. V.) the umbilical cord was delivered through the uterine wound and a control fetal blood sample was taken prior to the priming dose of amino acids. The heparinized samples were promptly centrifuged and the plasma samples were kept in the frozen state until time for analysis. Fig. 1 represents the protocol from one case (cesarean section), and illustrates the method used.

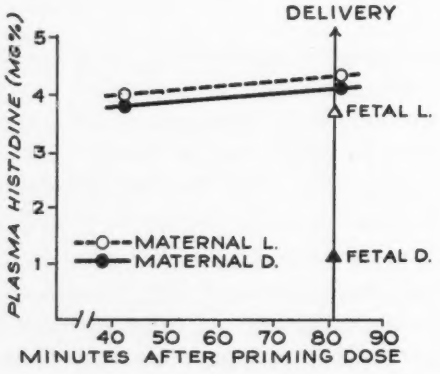

Fig. 1.—Representative protocol.

Determination of Total Histidine Concentration.—The colorimetric method previously described[13] was employed with minor modifications. Deproteinization of plasma was accomplished with heat and acetic acid (in place of perchloric acid), and the color was developed with diazotized p-chloroaniline. All samples were run in quadruplicate, using pure histidine additions as an internal standard. (A detailed description of each step, including the minor modifications alluded to will be sent to any investigator upon request.) When the colorimetric procedure was compared with the microbiological method, it produced values which averaged 0.6 mg. per 100 ml. higher. Recovery experiments at several concentration levels indicated that the microbiological assay gave true results for L-histidine. For that reason, the colorimetric determinations for total histidine were corrected by the difference between the colorimetric and microbiological values obtained on the control plasma samples for each individual.

Determination of L-histidine Concentration.—The natural L-isomer was determined microbiologically, with the use of the organism *Leuconostoc mesenteroides.* In separate experiments it was determined that the addition of widely varying amounts of D-histidine did not affect the assay for L-histidine. The quantities of D-histidine in plasma were determined by subtracting the L-histidine from the total histidine concentration. The mean L-histidine level for eight samples of fetal plasma selected at random was 2.1 mg. per 100 ml. Except in the one 9 minute experiment in which a fetal control level was actually obtained, this figure was assumed to be the fetal histidine concentration at the beginning of each experiment.

The maternal plasma histidine concentration present five minutes before delivery, as determined by interpolation, was compared to the fetal plasma concentration for the purpose of determining the ratios. After studying available data on the rates of transfer for radioactive sodium, the 5 minute lag was arbitrarily chosen as a minimal "appearance time" for histidine. In most instances the curve representing maternal histidine levels was relatively flat and this interpolation influenced the final ratio very little.

Results

In Table I the essential data for each experiment are recorded. The ratios of maternal to fetal histidine concentrations, as shown in columns 5 and 6, are plotted in Fig. 2 in order to illustrate the differential rates of transfer.

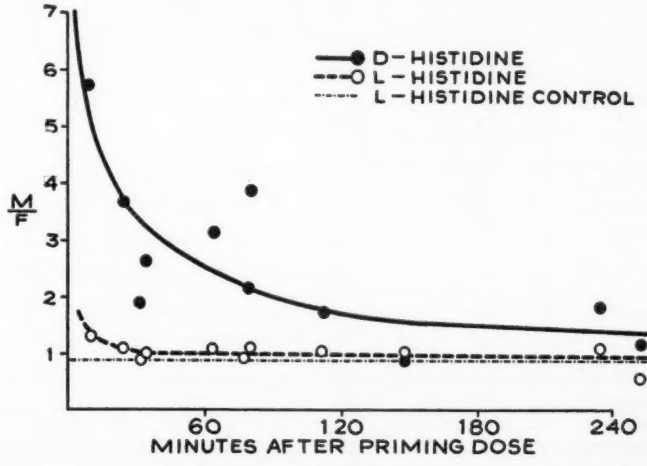

Fig. 2.—Maternal to fetal ratios for each isomer in each case. The control line represents the average ratio at time zero.

Comment

The subject of placental "permeability" has been discussed innumerable times in the medical literature, and has usually involved two questions: Can a given material cross the placental barrier or can it not? If it does, is it by a process of diffusion or by some other mechanism? With the evidence accumulating that even red blood cells and intact droplets of whole plasma may cross the placenta in both directions during the second half of human pregnancy, it seems self-evident that any molecule is capable of passing from mother to fetus provided that it is not destroyed during passage.

TABLE I. THE RELATIONSHIP OF MATERNAL AND FETAL PLASMA HISTIDINE CONCENTRATIONS

PATIENT	1. SAMPLE	2. TIME (MIN.)	3. L-HISTIDINE (MG. %)	4. D-HISTIDINE (MG. %)	5. MD/FD	6. ML/FL
L. V.	Maternal	0	1.6	- -		
	Maternal	5	5.0	4.4		
	Maternal	13	3.3	2.5		
	Fetal	0	2.0	- -		
	Fetal	9	3.9	0.8	5.73	1.33
O. C.	Maternal	0	2.1	- -		
	Maternal	18	3.9	2.2		
	Maternal	30	4.0	1.9		
	Fetal	24	3.7	0.6	3.67	1.06
A. D.	Maternal	0	1.4	- -		
	Maternal	14	3.1	4.2		
	Maternal	36	3.1	4.9		
	Fetal	31	3.2	2.4	1.91	0.97
V. L.	Maternal	0	1.5	- -		
	Maternal	19	2.7	2.1		
	Maternal	38	3.1	3.6		
	Fetal	34	3.2	1.1	2.64	0.91
M. S.	Maternal	0	2.1	- -		
	Maternal	44	4.1	4.7		
	Maternal	67	4.8	5.6		
	Fetal	64	4.3	1.7	3.12	1.06
U. H.	Maternal	0	1.8	- -		
	Maternal	36	3.2	4.9		
	Maternal	84	3.6	7.3		
	Fetal	79	3.8	3.1	2.16	0.95
B. I.	Maternal	0	2.1	- -		
	Maternal	42	4.0	4.0		
	Maternal	82	4.4	4.4		
	Fetal	81	3.7	1.1	3.94	1.17
V. D.	Maternal	0	1.7	- -		
	Maternal	53	3.6	6.1		
	Maternal	115	3.4	7.9		
	Fetal	111	3.3	4.4	1.73	1.03
G. J.	Maternal	0	1.6	- -		
	Maternal	22	4.0	2.1		
	Maternal	65	4.2	5.3		
	Maternal	97	5.0	2.3		
	Maternal	132	6.0	4.7		
	Maternal	150	5.5	4.6		
	Fetal	148	5.5	5.0	0.92	1.04
A. H.	Maternal	0	1.8	- -		
	Maternal	76	4.7	4.2		
	Maternal	139	5.9	7.1		
	Maternal	236	7.0	10.4		
	Fetal	234	6.2	5.5	1.86	1.11
V. J.	Maternal	0	1.8	- -		
	Maternal	33	2.8	3.6		
	Maternal	115	3.9	5.2		
	Maternal	197	4.5	6.1		
	Maternal	253	3.4	5.0		
	Fetal	251	5.9	4.3	1.18	0.59

It is hardly tenable, therefore, to inquire as to whether something in maternal blood can or cannot reach the fetus, or whether such a substance can cross by a process of diffusion. The pertinent questions today appear to be these: How rapidly does the substance pass? Is it destroyed or altered during passage? Is the rate of transfer sufficiently rapid to have any physiological significance? In addition to diffusion, is there another method of transfer which predominates?

The present investigation demonstrates that the unnatural isomer of histidine traverses the human placenta at an appreciable rate, and that it will come to equilibrium with the fetal blood in a matter of three or four hours. Presumably this transfer takes place by a process of diffusion, the rate at any given time being governed by the concentration gradient. Exact rates of transfer cannot be calculated because there are several other simultaneous processes going on. Among these are (1) renal excretion of the amino acid by both fetus and mother, (2) continued distribution into an unknown fraction of the total body water, and (3) a small rate of metabolism by D-amino acid oxidase.

It is obvious that the same rate of passive transfer must apply to the natural L-isomer, but it is quite evident that there is in addition an active transfer mechanism which proceeds at a considerably faster rate. This is illustrated by the fact that an equilibrium between maternal and fetal plasma concentrations is achieved within a matter of minutes. When no L-histidine is administered to the mother, the ratio between her plasma concentration of histidine and that of her fetus is 0.89, as determined by comparing the mean control values for maternal plasma with the mean of eight cord blood samples. The fact that equilibrium was achieved at approximately 1.0 under the conditions of our experiments is obviously due to the continued intravenous administration of the amino acid to the mother.

The fact that the total alpha-amino nitrogen concentration is significantly higher on the fetal side[7] suggests that perhaps all essential amino acids are transferred by an active process similar to that demonstrated here for histidine. Whether there are exceptions to this assumption must be determined by experiment for each individual amino acid. There is a strong possibility, furthermore, that specific groups of amino acids may compete with each other for active transfer, because this is true for renal tubular reabsorption. Inasmuch as maternal proteins are not transferred to the fetus in quantities which have any nutritional significance, and inasmuch as the rate of synthesis of fetal proteins is dependent in part upon the concentrations of essential amino acids, it becomes apparent that the whole problem of amino acid transfer assumes clinical importance with respect to intrauterine growth and fetal welfare.

Summary

The natural and unnatural optical isomers of histidine were infused into maternal veins for variable periods of time prior to delivery. The concentrations of each isomer were measured in both fetal and maternal plasmas. The

length of time required for the achievement of an equilibrium between maternal and fetal plasmas was used as an index of the relative rates of transfer.

The unnatural D-histidine required three or four hours to approach equilibrium whereas the natural L-histidine approached equilibrium within a matter of minutes. The data suggest that both molecules cross the placenta by a process of simple diffusion but that the natural isomer is transferred more rapidly by an additional active transport mechanism.

We are indebted to Leonard Olson for his faithful assistance.

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Discussion

DR. E. C. HUGHES, Syracuse, N. Y.—Dr. Page has shown his interest in histidine, an essential amino acid, first by reporting an increased excretion in normal pregnancy, second by describing the possible cause for its reduced excretion in pre-eclampsia, presently by determining the concentration of L-histidine and its unnatural isomer D-histidine in both fetal and maternal plasma.

He has demonstrated that L-histidine, an amino acid used for growth in the human being, reached an equilibrium between maternal and fetal plasma within minutes after injection into the mother, while the transfer of D-histidine took 3 to 4 hours to reach equilibrium. This experiment is important both academically and clinically. I will direct my discussion toward the two possible mechanisms which the author has proposed, by which such a transfer might take place.

The first mechanism is that these substances are pumped across the placental barrier. Such a pumping mechanism could occur in one of the following ways, or perhaps all of the following ways:

A. The placenta, by its anatomical formation, could serve as a fetal pump or accessory fetal heart. Krantz has demonstrated that there are circumferential and radial smooth-muscle fibers dispersed throughout the placenta. It appears that the placenta, perhaps, can pulsate, thereby aiding the flow of blood in the intervillous spaces and also supporting the intravillous circulation. Such action causes fluids to flow to and from the fetus.

B. The action of the contracting and relaxing uterus throughout gestation and particularly during labor may exert a positive pressure, pushing fluids and other substances toward the decidual-placental junction. There are certain experiments which may support this theory. Gardner, Walton, and Gonzales of our Center have found that the levels of

17-ketosteroids, adrenal corticoid, and pyruvic acid are higher in the plasma of the umbilical cords of babies during labor than of those delivered by cesarean section, although there is significant increase in the babies delivered by cesarean section. Hendricks, also, has demonstrated an increase in the lactic acid levels. This may mean that the contracting uterus forces these materials toward the fetal circulation and that the increased levels of these metabolic products are not entirely due to the increased fetal metabolic activity.

In this respect, the author has chosen the time of his experiment wisely and one may take his values as indicative of the relationship of maternal and fetal metabolism during the latter months of pregnancy. It would be interesting to repeat this experiment during labor.

C. The third possible pumping system could be called a biochemical or biochemical enzymal one. Recently it has been determined that adrenal corticoids play a vital role in the metabolism of the amino acids. At the end of pregnancy, the maternal circulation is flooded with large quantities of these steroids, making large quantities of nitrogenous material available to the fetus. On the other hand, the fetal concentration of these corticoids, until labor, is much lower—about one-half to one-fifth of the maternal quantity. It is very probable that this gradient of adrenal corticoid concentration between mother and fetus may help to explain the active transport of the natural L-histidine across the placental barrier. The unnatural D-histidine would not be incorporated in the fetal protein as readily—hence its relatively slow passage from mother to fetus.

As the second possible mechanism, the author has proposed that the trophoblastic epithelium is responsible for the transfer of these amino acids. Certain experiments tend to strengthen this theory. It is known that the trophoblastic epithelium changes its function at various stages of gestation. This is shown by the metabolism of sugar. During the first half of pregnancy, the chorionic villi are covered by two layers of cells, the outer syncytium and the inner Langhans cells or cytotrophoblasts. Each layer has a different function. The syncytium serves as a diffusing membrane passing sugar from the decidua, where it is found in abundance, through to the Langhans cells where it is metabolized and stored as glycogen. There is no storage in the syncytium. During this time, it can be said that the chorion serves as the fetal liver, particularly in view of the fact that the fetal liver does not perform the process of glycogenesis during this stage of gestation. The liver serves as a blood-forming organ at this time. Enzymes, which promote this metabolism, particularly alkaline phosphatase, are found in the syncytial cells and also in the endothelial cells of the vessels of the decidua. These enzymes help the diffusion of carbohydrates through the syncytium.

From the mid-portion of pregnancy certain histological changes take place in the chorion which adapt it for the diffusion of selected nutritive material. They are as follows:

1. The syncytial covering of the villi becomes exceedingly thin, consisting of one layer of cells.

2. The capillaries within the villi approach the surface of the villi coming in closer contact with the maternal decidua.

3. There is a marked increase in the secretion of enzymes by the syncytium, particularly the phosphatases. These enzymes are needed for carbohydrate and nucleoprotein metabolism. There is no storage of these materials and the fetal liver assumes the role of glycogenesis.

4. The trophoblastic epithelium becomes highly selective. This is shown in this experiment by the fact the L-histidine is allowed through easily while holding back the D-histidine.

5. The chorion chemically produces material which enhances the passage of carbohydrates, proteins, and especially amino acids across its barrier.

It is possible that both systems proposed by the author work together, causing the transport of these essential amino acids and other substances from the maternal decidua to the fetus. The fetus, through its own endocrine, enzyme, and metabolic processes, can produce its own intrauterine growth.

DR. E. STEWART TAYLOR, Denver, Colo.—My contribution as one discussing this paper will be to interpret the importance of the amino acid histidine to this audience, and to elucidate the significance of this experiment and other experiments of Dr. Page having to do with the metabolism of this essential amino acid in normal and abnormal pregnancy.

In the course of Dr. Page's studies he has been interested in placental metabolism as it may relate to the eclamptogenic syndrome. This interest could not help but invite his attention to the work of Honda who in 1923 reported histidine in the urine of pregnant women as a rather constant finding. As a matter of fact, the histidinuria was such a reliable accompaniment of normal pregnancy that Voge proposed a chemical test on the urine for histidine that could be used as an aid in the diagnosis of pregnancy. The histidinuria test was reported as being approximately 85 per cent accurate in the diagnosis of pregnancy.

The cause of increased histidine in the urine of a pregnant patient is hypothetical. Dr. Page believes, on the basis of previously reported work of his group, that pregnancy causes an increased renal clearance of histidine, secondary to a diminished rate of renal tubular reabsorption. This may be part of the explanation since we know that there are changes in the kidneys' ability to handle other elements and compounds during normal pregnancy. Examples are the well-known disability of the pregnant woman's kidney to excrete water and salt in the same fashion as when the patient is not pregnant. It seems to me that there is an additional explanation for histidinuria during pregnancy. That reason has to do with the character of the amino acid histidine as an amino acid essential to growth. Histidine is not an essential amino acid for the adult organism. It is an amino acid essential to the growing human being. The process of growth flourishes best in biology when there is a surfeit of essential elements available to the growing organism. To me the histidine in the urine is simply an overflow to the maternal circulation of what is not assimilated by the fetus and its membranes during its period of rapid growth.

Dr. Page's investigations on histidine led him to investigate histidinurina as influenced by pre-eclamptic toxemia. He confirmed that histidine excretion was reduced in the urine of the patient with pre-eclampsia. He has been able to prove that the reduced excretion of histidine in the patient with pre-eclampsia is a manifestation of abnormal kidney function, and not a basic change in the metabolism of this amino acid. He has not been able to associate reduced histidine in toxemic pregnancy with the cause of toxemia of pregnancy.

The current experiment was designed to determine whether the placental membrane would transfer the natural isomer of histidine across the placental barrier faster than the unnatural isomer. There is no question that the natural isomer entered the fetal circulation at a much faster rate than the unnatural isomer of histidine. From these data it is probably safe to presume that placental cells or enzymes have speeded the transport of natural histidine, whereas such a vital activity does not participate when the unnatural isomer crosses to the fetal circulation. In order, however, for any biophysical process to be proved to involve an active transport system it is necessary to demonstrate that energy has been expended by the membrane itself. I am sure that Dr. Page is aware of this and is willing to accept his experiment as indirect evidence of an active transport system in the placental membranes for the essential amino acid histidine in its natural form. The measurement of oxygen consumption by the placenta to prove finally a vital action in the placenta in regard to the passage of amino acid molecules could not be done on the human subject. It would have to be done with a Warburg apparatus using tissue slices of placenta so that the actual utilization of oxygen by the placental tissue could be measured. If energy were used in the transport, this would be final proof of an active transport mechanism.

One other thought has occurred to me concerning this experiment. Dr. Page has demonstrated that an unnatural isomer of an amino acid passes the placental barrier at a rather delayed rate, three to four hours. Would it not be possible to use this knowledge to prepare an analgesic drug attached to an unnatural isomer of histidine? The analgesic drug could benefit the mother but could not enter the fetal circulation until much later. Such a chemical union has been successful in the case of the protamine insulin which is a slow-acting insulin.

DR. HOWARD TAYLOR, JR., New York, N. Y.—I should like to ask Dr. Page for the reason why he assumes that his observations cannot be explained as a transformation in the placenta of one type of amino acid to the other, rather than a difference in the rate of transfer of the D-amino and L-amino acids.

DR. PAGE (Closing).—Dr. Hughes suggested the possibility of some type of mechanical action which pumps materials across the placenta. This can be ruled out, I believe, by the fact that the maternal to fetal ratios for different substances vary in opposite directions. Those materials which constitute essential "building blocks" for fetal synthesis, such as the water-soluble vitamins, amino acids, and nucleoproteins, are higher on the fetal side. On the other hand, more "adult" compounds such as lipids, fibrinogen, and many other molecules are higher on the maternal side. A mechanical pump should not show favoritism such as this. In the case of amino acids, we are left with the concept of an enzymatic carrier system.

Some carrier systems do not require oxygen but utilize other forms of energy. It might be difficult to study transport systems (as opposed to synthesis, for example) in the Warburg apparatus. Dr. Taylor's question about the change of one isomer into the other merits serious consideration. This would require the sequential action, if I am not mistaken, of D-amino acid oxidase and a transaminase. Whether both enzymes are present in the human placenta may not be known; but assuming that they are, I believe that a calculation of rates would reveal this to be a very slow process. I do not think that it could account for the very rapid appearance of the natural isomer on the fetal side.

The renal tubules actively reabsorb the natural amino acids by means of an enzymatic carrier system and reject the unnatural forms. I think that there must be a parallel system in the placenta.

Dr. Bruns, in his paper, alluded to the cessation of fetal growth in a case of pyelonephritis. We have all seen this in cases of glomerulonephritis and during pre-eclampsia. In recent years, much emphasis has been placed upon fetal hypoxia and oxygen transfer problems. This may, of course, result in damage to the fetal brain, but I am not at all sure that oxygen controls growth rates. The rate of fetal growth is dependent upon the rate of synthesis of new tissue. To a large extent, this is dependent upon protein synthesis. The latter, in turn, is largely influenced by the concentrations of essential amino acids in proper proportions. According to mass laws, the higher the concentration of these "building blocks" the more rapid the synthesis. The maintenance of a high concentration of amino acids on the fetal side depends upon the integrity of the enzymatic carrier systems postulated today. Villee has already demonstrated that in pre-eclampsia the essential amino acids are lower in fetal blood and that the differential gradient which favors the fetus is lost. This may be why babies stop growing under abnormal circumstances. The interference with the carrier systems might well be due to uterine ischemia. At least I have thought so since propounding the placental ischemia hypothesis in 1938, and developments of the past 18 years have served only to strengthen my belief that an impairment of the uterine circulation is of primary importance not only with respect to the etiology of the toxemias and the transport of oxygen but to the transfer of essential "building materials" to the baby.

THE EVALUATION OF THE BASAL CELL IN THE RADIOSENSITIVITY STUDIES OF CARCINOMA OF THE CERVIX*†

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(From the Stritch School of Medicine of Loyola University)

THE objective analysis of the individual case of cervical carcinoma must include consideration of the radioresistant character of certain of these lesions. Establishment of a binary mode of therapy has been deferred pending the advent of some means of delineating unequivocally, which, of any given number of cases, will or will not respond to radiation. In 1947[1] the Grahams presented a study that implied great promise of the solution of this most important problem. The contemporary investigations by other workers in the field have been divergent in their confirmations. In the current literature, four reports are critical of the method,[2] three support it in a general way,[4] and two are in accord.[5] In analyzing the areas of contention, certain difficulties become apparent; namely, lack of standardization of techniques, confusion in interpretation of cellular changes, and a want of adequate correlation with the clinical course of the patient.

During the past year, in attempting to standardize our techniques in evaluating radiosensitivity of carcinoma of the cervix by cytological smear, we have become aware of certain reactions, both actual and implied, of the basal cell of the cervicovaginal epithelium. Our purpose in presenting these findings is to establish the basal cell as the denominator in the designation of good or inferior response to therapy.

Methodology

The original differential counting method of the Grahams[1, 3, 6] was modified by counting 100 consecutive benign epithelial cells in two or more smears after screening the smear under low power. Sensitization response (SR) and radiation response (RR) were tabulated on the basis of four distinct changes (Plate I): (1) vacuolization of the cytoplasm, (2) enlargement of the cell, (3) nuclear changes, (4) multinucleation.

Certain other changes, namely, change in cytoplasm color, cytoplasmic fibers, and bizarre forms occur inconsistently but, when they do so, they may be predominant enough to influence the RR count. In a typical smear showing good SR the prevailing change was vacuolization followed next in frequency by nuclear changes. The other cytological features were minimal. Fig. 1 shows the proportionate distribution of these SR responses. It was our impression that the changes taking place in the basal cells prior to irradiation are

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**Fellow, American Cancer Society.

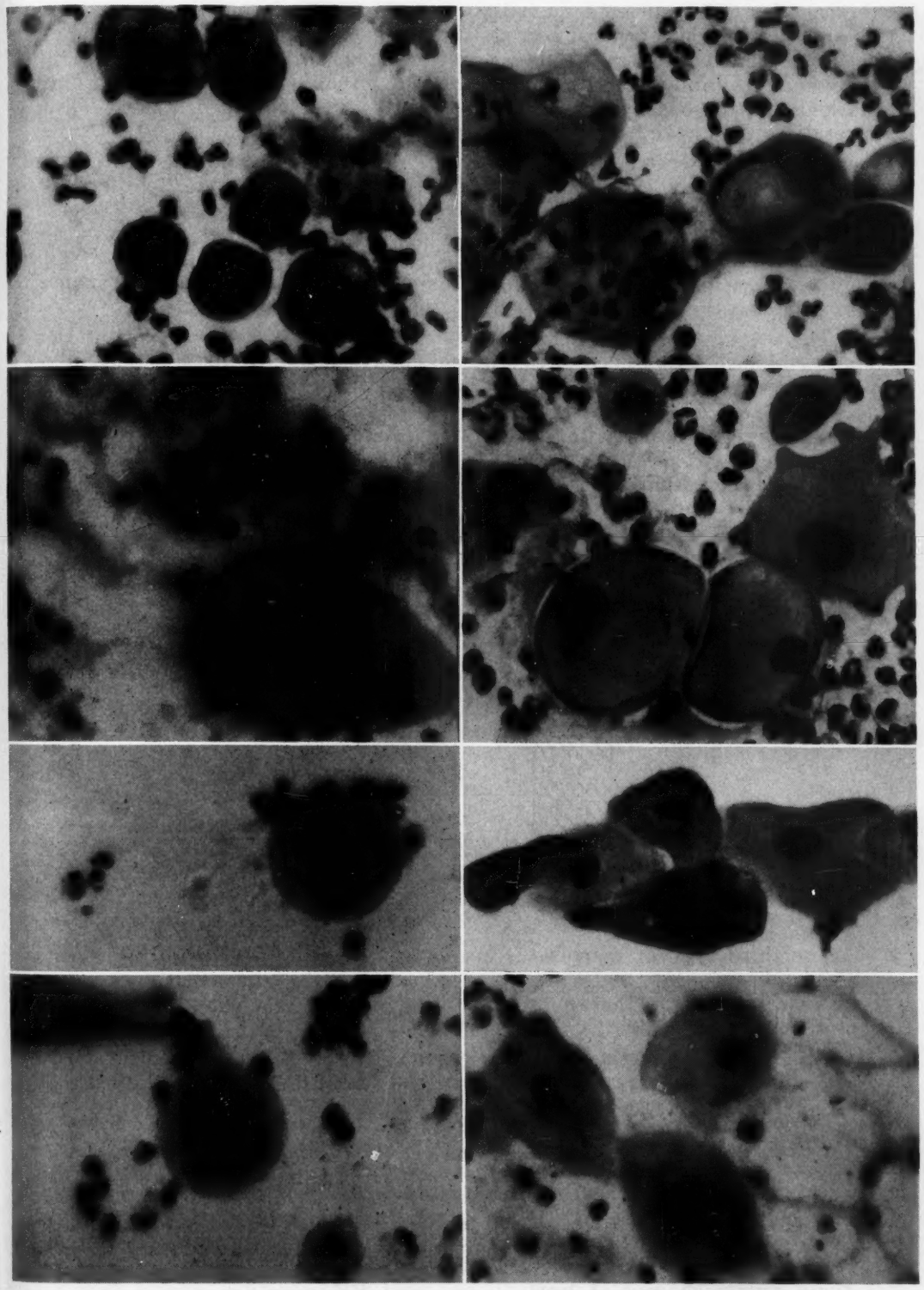

Plate I.—Photomicrographs showing the similarity of response before and after treatment. In the left-hand column are cases prior to treatment (SR) and in the right-hand column are those during treatment (RR). I and I,*A* show vacuolization; II and II,*A*, cell enlargement; III and III,*A*, nuclear change; IV and IV,*A*, multinucleation.

the same as those initiated by radiation therapy. Their incidence represents a partial insight into general host resistance but not specifically to malignancy, since it is not uncommon to find SR in routine screening smears. In general, these changes take place in all layers of the epithelium, but earliest and most markedly in the basal layers and infrequently in the cornified layers. These several features have been alluded to in studies by the Grahams.[7, 8, 9]

We have observed four characteristic responses to radiation, principally reflected in the basal cells. The first response is a typically good response showing basal-cell vacuolization and nuclear change within the first two weeks of therapy. These basal cells account for 62 to 72 per cent of the total radiation responses. After four weeks of therapy, 75 to 84 per cent of the basal cells show response and these account for 89 per cent of the total radiation response. This type of pattern is accompanied by clinical regression of the lesion.

The second type of response is atypical in that half of the cell population shows response after seven days with no change in the comparative distribution of cornified and basal cells. Even so, the changes in the basal cells make up 88 per cent of the total response. After four weeks of therapy there is a marked increase in radiation response throughout the cell population with basal-cell changes accounting for 85 to 91 per cent of the total response. Here, too, clinical regression of the lesion occurs.

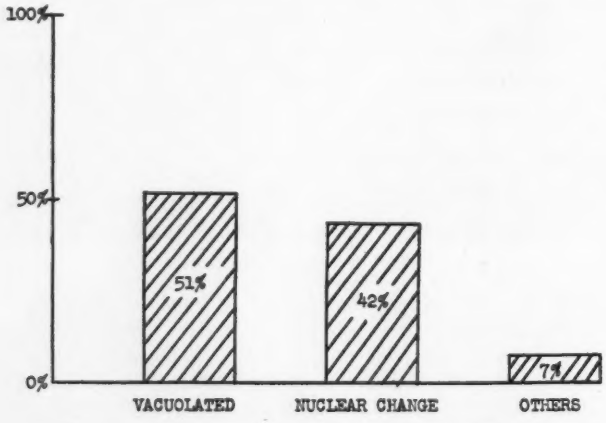

Fig. 1.—Proportionate distribution of SR changes.

The third type of response is a delayed response cytologically but with clinical regression of the lesion. There may be only slight radiation response until after 35 days of therapy. When the response takes place, 95 to 100 per cent of the response is in the basal cell.

A fourth type of response may be considered a refractory response wherein there is slow disappearance of malignant cells from the smear and an associated poor radiation response after two weeks of therapy.

Material

Thirty cases of cervical carcinoma were studied by serial smears before, during, and after treatment. Each patient received a tumor dose of 7,000 to 9,000 gamma roentgens by means of 1,000 kv. x-ray and fractionated intracervical radium. Patients were classified as having a good radiation response if their counts showed at least 75 per cent RR sometime during therapy. Counts with no more than 60 per cent RR were classified as poor response.

This is in accordance with the Grahams'[4] recommendations. We have also classified the cases according to basal-cell response and considered the basal-cell response as good if it was 45 per cent or better of the total radiation response and poor if the count represented 30 per cent or below.

Results

Table I shows that in general good radiation reaction was paralleled by a good basal-cell response. The extent to which the basal-cell response accounted for the total radiation reaction is shown in Fig. 2, the range being from 2 per cent to 98 per cent, with all but 9 instances contributing better than 45 per cent.

TABLE I. COMPARATIVE INCIDENCE OF RADIATION AND BASAL-CELL RESPONSE

Total number of cases			30 (100%)
Number showing good RR*		22 (73%)	
With good BR*	20 (67%)		
With poor BR	2 (7%)		
Number showing poor RR		8 (27%)	
With good BR	3 (10%)		
With poor BR	5 (16%)		

*RR, Radiation response. BR, Basal-cell response.

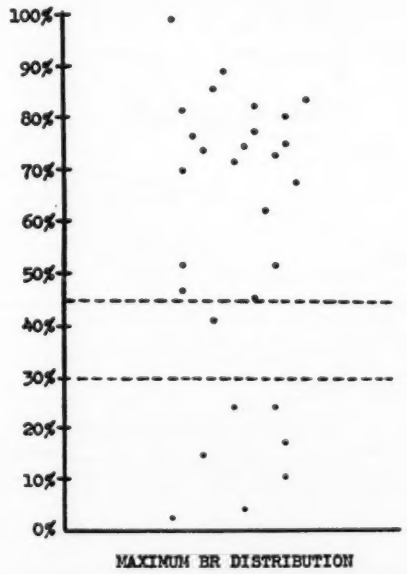

Fig. 2.—Maximum range of basal-cell response.

The index of host resistance as indicated by basal-cell response is more apparent in the figures presented in Table II. The term immediate recurrence refers to cases of persistent disease as contrasted with cases of delayed recurrence. It is to be noted that the lowest rate of immediate recurrence is associated with good basal-cell response, while the patients showing a poor basal-cell response had a 57 per cent immediate recurrence rate as shown in Table III.

Many of these findings are best demonstrated in the graphical representation of specific cases. Fig. 3 shows the representation of a typically good response with radiation and basal response paralleled and a depression of the more mature elements.

We have had 2 patients who showed a good radiation response and poor basal response. Fig. 4 shows the distribution of cells of one case during therapy. Her initial count showed only 30 per cent basal response and this steadily declined during therapy. The patient had a questionable clinical improvement for a few weeks but eventually succumbed to a generalized carcinomatosis. The second patient showed a delayed recurrence and was subjected to radical surgery six months after treatment.

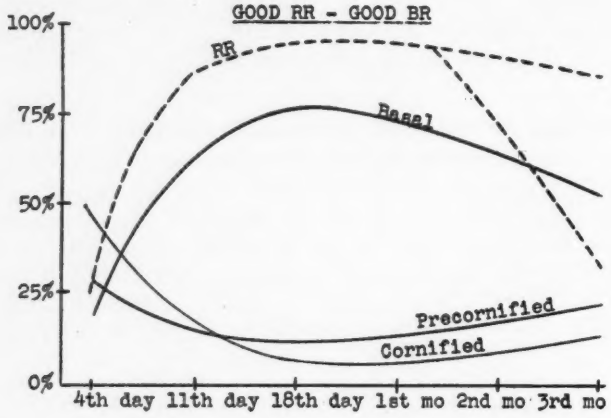

Fig. 3.—Graphic representation of a typical good response.

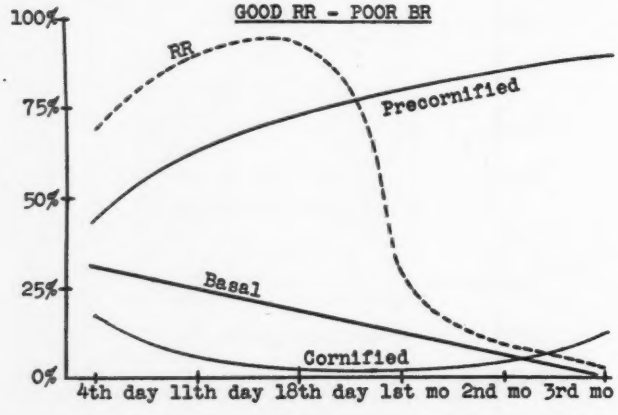

Fig. 4.—Graph depicting good RR and poor BR.

TABLE II. RELATION OF IMMEDIATE RECURRENCE TO ADEQUATE BASAL-CELL RESPONSE AND RADIATION RESPONSE

Total number of cases			30 (100%)
Number with good RR and BR		20 (67%)	
With immediate recurrence	2 (7%)		
Number with good RR and poor BR		2 (7%)	
With immediate recurrence	2 (7%)		
Number with poor RR and BR		5 (17%)	
With immediate recurrence	2 (7%)		
Number with poor RR and good BR		3 (10%)	
With immediate recurrence	0 (0%)		

One would expect those cases which show both a poor radiation and poor basal response to show no host resistance whatsoever. Nevertheless, 3 out of

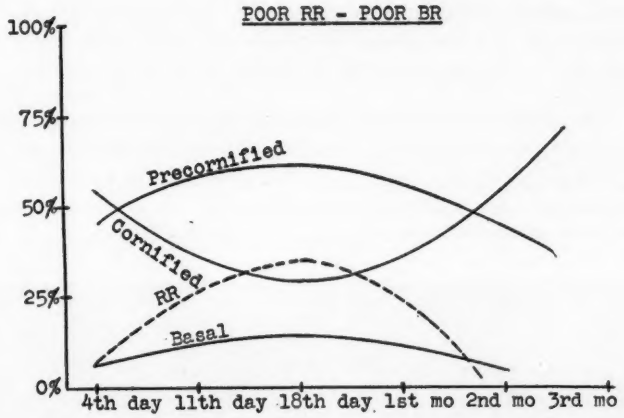

Fig. 5.—Cellular distribution in a generally poor response.

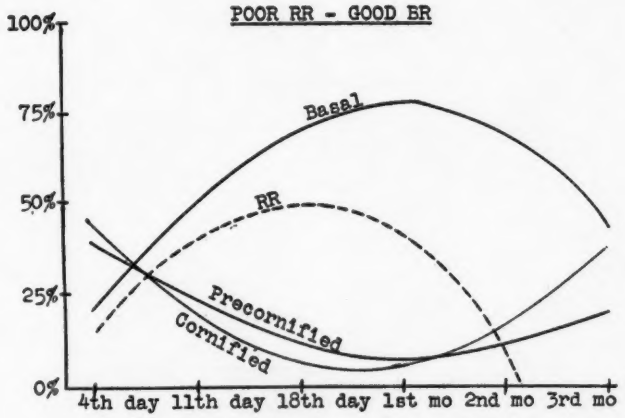

Fig. 6.—Demonstrating good BR in spite of poor RR.

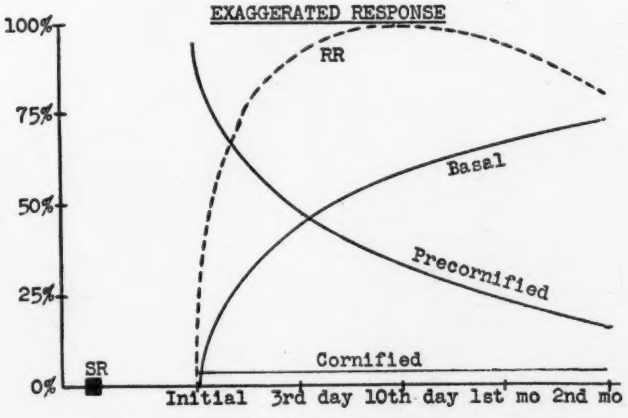

Fig. 7.—Graph depicting exaggerated response.

5 patients have remained without immediate recurrence. Fig. 5 shows some activity in the more mature cells but no adequate radiation effect. In the final example, the influence of a good basal response in spite of a poor radiation response is demonstrated. None of these 3 cases showed immediate recurrence.

TABLE III. RELATION OF BASAL-CELL RESPONSE AND IMMEDIATE RECURRENCE

Number of patients with good BR		23 (100%)
Number with immediate recurrence	2 (9%)	
Number of patients with poor BR		7 (100%)
Number with immediate recurrence	4 (57%)	

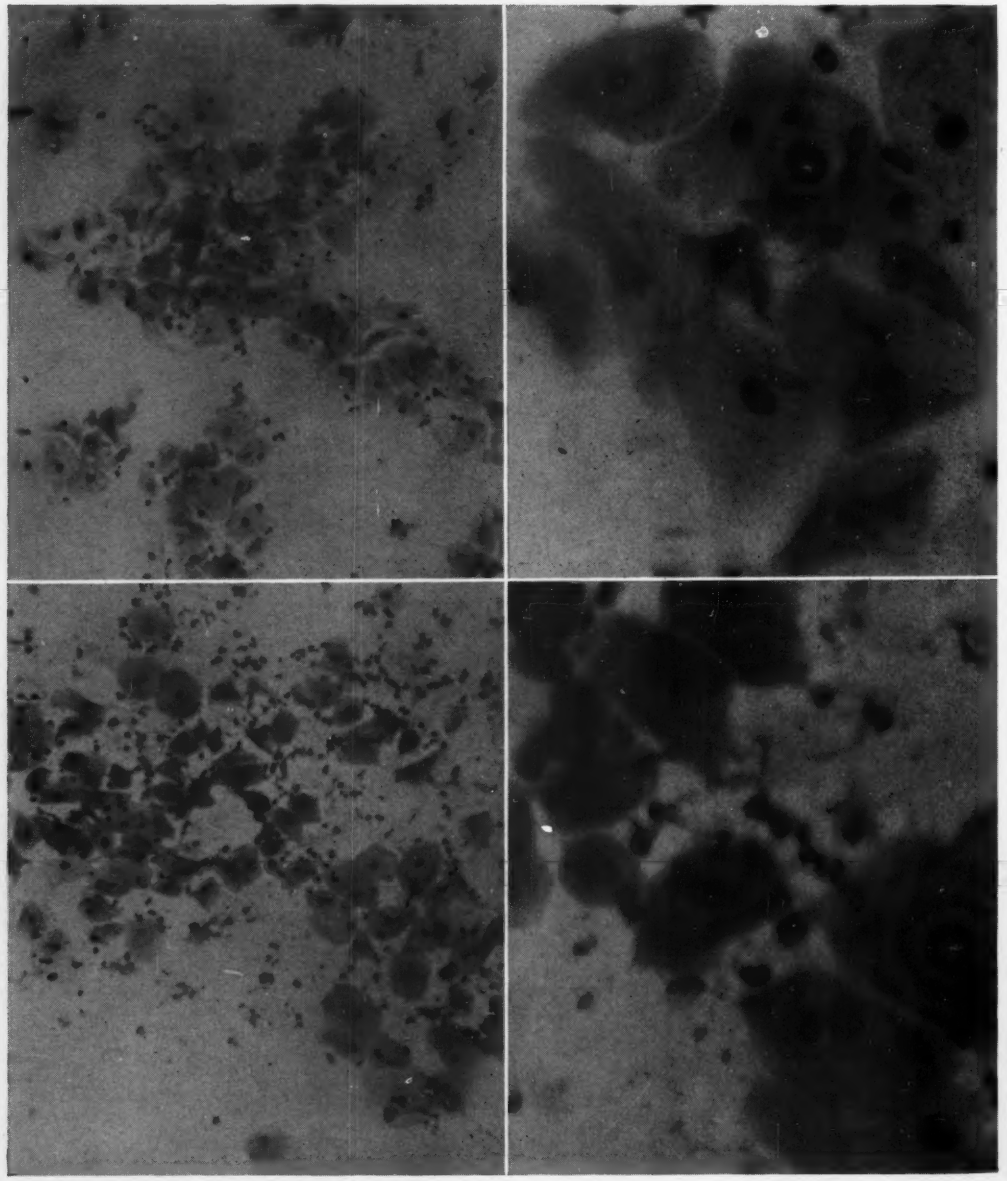

Plate II—Photomicrographs showing an exaggerated response. I and I,A, prior to treatment; II and II,A, after administration of 520 r.

Comment

The several elements of this study may be correlated by the example of a single case.

Mrs. B. W., aged 50 years, gravida 0, para 0, was referred for treatment of a Schmitz Group I lesion. Her initial smear (Plate II) showed a differential count of 95 per cent precornified cells with no SR. After 525 r tumor dose, she showed a basal response of 44 per cent with an RR of 92 per cent. With another week of treatment these figures rose to 59 per cent and 100 per cent. Her treatment was discontinued because of severe enteritis and a febrile reaction. Nevertheless, one and one-half months after treatment her basal-cell response had risen to 70 per cent and the RR had dropped to 80 per cent. Biopsy was unable to show the presence of tumor. Fig. 7 shows a graphical representation of this response.

Summary

In the following of 30 patients under treatment for carcinoma of the cervix by serial cytological smear studies, it was found repeatedly that the sensitization response and the radiation response were reflected chiefly in changes of the basal cells. We feel that SR differs in no way from RR except for the inciting factor, with the implication that the one response is an index of general host resistance not specific in malignancy, and that radiation tends to stimulate, suppress, or not to affect this index. We are forced to assume, therefore, that RR is a more accurate evaluation of the success of radiation therapy and that in this radiation response a satisfactory basal-cell response represents the real effort on the part of the host to control the disease. In our experience a good basal response ranges from 45 per cent and over, while a poor response is found below 30 per cent. Of more prognostic significance than any set figures, however, is a progressively increased basal-cell response during the course of therapy.

Conclusions

1. Thirty patients under treatment for carcinoma of the cervix were studied by serial smears before, during, and after therapy.

2. The cellular changes commonly considered to be evidence of radiation effect were found to be present in the preirradiation smears.

3. The principal cell involved in showing response is the basal-cell and when this finding is in excess of 45 per cent of the total cellular reaction, the response is considered good. Below 30 per cent, it is considered poor.

4. Clinical regression of the lesion is more closely related to good basal-cell response than to any other findings.

5. The behavior of the basal-cell activity before and during treatment suggests that it serves as an index of host resistance.

6. Radiation characteristically produces, in general, four types of responses which may be determined by differential counting.

The invaluable assistance of Mrs. Ramona Aiken, technician, is gratefully acknowledged.

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Discussion

DR. DANIEL G. MORTON, Los Angeles, Calif.—What proportion of cancers of the uterine cervix prove to be resistant to radiation is not precisely known. However, it is generally agreed, I believe, that the majority, perhaps 85 to 90 per cent, of cervical cancers are actually reasonably sensitive to irradiation and that our treatment failures are due principally to the extension of the growth to a degree which prevents the delivery of a cancerocidal dose of radiation to all areas rather than to radiation resistance. Nevertheless, a means of determining radiation sensitivity before treatment, or even early in the course of radiation therapy, would be an important advance. Such knowledge would permit us to resort to surgery where radioresistance had been indicated at a much more propitious time than is currently possible and would add significantly, though I don't know just how much, to the over-all salvage.

I was much interested in the observations reported by Dr. Smith and his collaborators. I believe them to be too few in number to permit final conclusions, however, in view of the many variables involved which could have a bearing on the correlations arrived at. I should like to bring to your minds the several most important variables which must be taken into consideration in evaluating work of this kind:

1. The cellular changes upon which the results depend are subject to marked variation in interpretation (e.g., cell size).

2. The necessity for choosing arbitrary percentage figures above which or below which occurrence of the cellular changes indicates radiosensitivity or radioresistance results in a rather uncertain sort of calculation at best.

3. Variability of the cell population in smears, depending as it does upon such factors as age, degree of estrogenation, cyclic hormone activity, possibly the concentration of hormones other than sex hormones, presence or absence of trichomonads and possibly of other invaders, bacterial, viral, or otherwise, must certainly be included in the equation.

4. The clinical stage of the disease at the time of treatment unquestionably has a marked influence upon the results.

We are left then with a conclusion based upon an aggregate of cell changes subject to marked differences in interpretation occurring in a percentage of counted cells, which exceeds or falls below arbitrary figures, without reference to the various factors which can affect the character of the cell population, such as age of patient, degree of estrogenation, presence or absence of local infections, and without reference to that most potent of all determinants, the stage of the disease. It was manifestly impossible for Dr. Smith to control variables of this kind, important as they are, on the basis of observations made in 30 cases. It is to be hoped that his series can be extended on and on until the time when the accumulated volume of information will eliminate the question marks produced by the variables.

Regarding the emphasis upon changes in the basal cells we would only point out that the proportion of such cells in smears from younger women might be so small as to preclude a satisfactory evaluation at the onset of treatment. Late in the course of, or after, radiation therapy we would expect an increase in such cells due to the suppression or destruction of ovarian function. We would agree with Dr. Smith that where present in sufficient numbers the basal cell is the best single indicator of the changes described for SR and RR.

I feel less certain than the essayist of the validity of the Grahams' theory that the changes in the vaginal cells, which Dr. Smith has described for us, constitute a measure of "host resistance." I do not say that this is not so but merely that we must continue to

regard it as theory at this time. The term "host resistance" presumably refers to resistance to invading infectious agents. Is there a relationship with cancer? Is there a relationship with radiation? Is it justifiable to refer to "host resistance" as if this encompassed resistance to cancer? To me it is very disquieting that those with "good SR" have usually been those who had early growths. How come? Why not an equal incidence in those with advanced cancer? In other words, can we rely upon the correlation of good results with good SR, and of poor results with poor SR? I do not raise these questions in the spirit of idle criticism, but rather because we have been confronted with the same problems and have learned to appreciate the weak points. In our laboratories we are making similar efforts to assess radiation sensitivity.

I believe that the direction of Dr. Smith's observations is excellent and I hope that the suggested cytological-clinical relationship will prove to be valid, but I do believe that validation will require many more cases, in which the patients have been followed for more than five years and the results broken down into appropriate age, stage, stage of cycle, etc., groups before a completely satisfactory answer can be found.

DR. JOSEPH A. HARDY, St. Louis, Mo.—Dr. Smith has referred to the impression he and his co-workers have had that changes taking place in the basal cells prior to radiation are the same as those initiated by radiation therapy; or, as he restates it in his summary, "SR differs in no way from RR except for the inciting factor, with the implication that the one response is an index of general host resistance not specific in malignancy, and that radiation tends to stimulate, suppress, or not to affect this index." It seems to me that in these observations lies the suggestion as to the direction research must take if we are to reach our goal of understanding which cervical cancers will respond to radiation and which will not.

Since the Grahams, in 1947, reported their observations on the effect upon the vaginal cells of radiation of cervical carcinoma their methods have been adopted, refined, and adapted by many investigators. In their most recent report the Grahams have suggested measurement of cell size in the vaginal smear as a prognostic sign of response to radiation. Dr. Smith tells us that the behavior of the basal cells will indicate the degree of sensitivity of the carcinoma which has been radiated. I hope that I may not seem entirely facetious if I say that all this reminds me somewhat of the definition of a barometer as an instrument which tells us what kind of weather we are having.

From the viewpoint of the clinician the determination of the radiation response in a given patient must come, in all too many instances, after he has committed himself to a mode of therapy. And those of us who have attempted surgical intervention in the patient who has received extensive radiation are aware of the extreme difficulty of tissue handling and of tissue healing with which we must contend. Dr. Smith has not classified the 30 patients who made up his material as to the clinical stage of their disease. This is quite understandable since his concern was merely with their response to radiation. But for the clinician who chooses between surgery and radiation for his patient, such factors as clinical stage, age of patient, her bodily habitus, physical condition, geographic location with relation to possible radiation installations, availability of cytologists equipped with the special skills necessary for reliable diagnostic and prognostic studies—all of these and other considerations will be pertinent to his decision.

DR. SCHMITZ.—We have all been searching for some time for a means of determining the sensitivity and resistance of tumors. To present to you 30 cases seems to be an imposition; we must realize, however, that each of these 30 patients was subjected to numerous smears and that each day smears were taken there were three counts of 100 cells. We felt, therefore, that in the large number of counts that we have on 30 patients we had established for ourselves sufficient evidence so that we would transmit this information to you, who I am sure will investigate it with us and one day evaluate it pro or con.

The sensitivity of tumors varies with the size and the migration of the tumor cells, so that the information that we are going to gather by this type of study will always be confined to the primary site of the tumor, and will not tell us what has happened to the sensitivity of the tumor when it has entered into a lymph node. I am quite sure that as we go along with our early cases of cervix cancer, our Group I and II cases, and subject the patients with poor response to surgery, we are going to improve our over-all end results markedly. We had been doing this for some period of time before we began the rhythmic and regular counts and it is beginning to show us a very definite improvement in the patients whom we have irradiated and in those we have selected for surgical treatment.

DR. SMITH (Closing).—Dr. Morton emphasizes an important thing when he reminds us that the great majority of the patients with carcinoma of the cervix who come to us for treatment are radiosensitive and can be treated satisfactorily by this agent, and that this whole problem of radioresistance and radiosensitivity still involves only a small proportion of patients.

Our laboratory, almost from its inception, has been constantly struggling to simplify techniques and interpretation. Some day we may have a simple differential stain for carcinoma cells that will enable any general practitioner to make a diagnosis at his office. But by attempting to simplify we have gone to the basal cells.

In a sense this paper is pessimistic with regard to the ability of the laboratory at the present time to tell you in advance whether this patient is or is not going to respond to therapy, because we believe that the best way to determine radiosensitivity is by examining the basal cells after therapy has been begun.

RESULTS AFTER CONSTRUCTION OF ARTIFICIAL VAGINAS*

DAVID NYE BARROWS, M.D., NEW YORK, N. Y.

(From the New York Polyclinic Medical School and Hospital)

MY EXPERIENCE with the surgical creation of an artificial vagina, where the entire cavity is congenitally absent, has been based upon the application and modification of the operation described many years ago by Kirschner and Wagner.[2] Their procedure consisted essentially in dissecting an adequate channel, lining it with thin skin grafts, and then maintaining patency either with a prosthesis or by coitus.

We never consider creating such a channel before the patient has reached adult stature, except in an emergency created either by hematocolpos or hematometra. If marriage has not already taken place, I plan to operate where possible from one to three months prior to that event, so that patency will be permanently established and maintained. By cooperation of the patient in the faithful use of a dilator, we have found that we can establish and maintain adequate depth and capacity.

My belief in the value of such an operation is definite, because it helps to cure, or at least relieve, the serious feeling of inadequacy which often produces subsequent serious psychic disturbances.

The first case reported occurred on the service of the late F. C. Holden, although he did not himself favor the operation on principle. The operation therefore was carried out when Dr. Holden was on vacation. Under such conditions, I had to select a technique free from hazard to the patient. In this patient and in others of the first group of cases, we cut our thin skin grafts with a razor-type of blade, later using a dermatome to prepare a graft 8 by 10 cm. in size. These larger grafts were much easier to handle. We sewed or tied them to the prosthesis with fine plain catgut.

After Counseller and others reported definite success with plastic or other prostheses without skin grafts, I gave up the use of skin grafts entirely. My principal reason for abandoning skin grafts was to avoid the visible body scars and the subsequent embarrassment to the patients which might tend to increase, or at least perpetuate, the psychic trauma I was trying so hard to avoid.

Technique of Operation

It is very helpful to explore the abdominal situation by laparotomy and, at present, I am employing a double operating team, forming the vagina while the abdomen is open.

My present technique I consider very simple. A transverse incision is made through the mucosa of the vestibule. With a sound or firm catheter in the urethra and a finger in the rectum, the area between the latter and the bladder is dissected in the line of the incision, either by finger or other blunt

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dissection to a depth of 9 to 10 cm. and a width of 6 to 8 cm. Penetration of the peritoneum is avoided, though it can be easily mobilized under direct vision toward the rectum to achieve additional depth, if necessary. This is where the simultaneous laparotomy is most valuable. Obstructing fibrous bands may have to be cut through. The prosthesis is then inserted and secured in position by closing the vulva temporarily with four or five nonabsorbable sutures. These sutures are removed on the tenth postoperative day. A Foley catheter is also left in the bladder for the same period of time.

As a general rule, the prosthesis is worn twenty-four hours a day for three months, then at night for 6 to 9 months, being given up earlier at the beginning of regular coitus.

Associated Anomalies

To date, I have not been fortunate enough to have had a case in this series with a functioning uterus. One of our patients had developed a hematometra at the age of 15 years with an abdominal mass the size of a four months' gestation, for which a total hysterectomy had been performed.

Without exception, these patients have shown satisfactory development of all external secondary sex characteristics and have professed normal libido. With one exception, they have all had two ovaries, two tubes, and well-developed round ligaments. The one exception had a uterus unicornis with a single large ovary and one highly convoluted tube.

There have been 2 cases of uterus duplex unicornis rudimentarius. One of these patients had a rudimentary cervix and two small proportionately sized uterine arteries. Our usual case has shown a slender fold of peritoneum joining the junctions of the tube and round ligament on either side of the pelvis, or from one uterine horn to the other.

I have encountered 2 fused kidneys; 2 patients with one pelvic kidney with the other kidney in its normal position; one with marked asynclitism of the pelvic girdle; one with double ureter, two kidneys in the pelvis, and a marked spina bifida. Thorough x-ray workup is therefore essential in all these cases before surgery is attempted.

Types of Prostheses

Four cases with skin grafts were managed with the use of rubber sponge prostheses; 2 with natural rubber and 2 with synthetic sponge, when the natural became unavailable (Table I).

TABLE I. VARIOUS PROSTHESES USED TO CONSTRUCT AN ARTIFICIAL VAGINA WITH SKIN GRAFTS

CASE NO.	AGE	PROSTHESES	SKIN GRAFTS	RESULT	LAST CHECKUP
1	20	Sponge rubber	Narrow thin strips	Excellent	10 years; ok.
2	26	Sponge rubber with drain	Narrow thin strips	Excellent	5 years; ok.
3	23	Synthetic rubber	Large thin graft, 8 by 10 cm.	Excellent	10 years; ok. Ring scar at 10 cm.
4	20	Synthetic rubber	Large thin graft, 8 by 10 cm.	Fair	3 years. Good after circular scars were cut and dilated
5	21	Pine wood, 1⅞ inches diameter	Large thin graft, 8 by 10 cm.	Excellent	5 years; ok.
6*	26	Dental molding compound over tin	Thin strips	Excellent	10 years; ok.

*To enlarge congenitally narrowed vagina. Case 6 only.

In the cases done without grafts (Table II), I have used the Bakelite mold of Counseller in 4 cases and in 4 others plain 2 by 2 inch white pine, turned down by our hospital carpenter to a diameter of from 1⅝ to 1⅞ of an inch. On occasion I have used laminated light wood, or balsa wood which is very light and easily shaped with a penknife.

TABLE II. PROSTHESES USED TO CREATE ARTIFICIAL VAGINA WITHOUT SKIN GRAFTS

CASE NO.	AGE	PROSTHESES	GRAFT	RESULT	LAST CHECKUP
7	20	Pine wood, 1⅞ inches diameter	None	Excellent	1½ years; ok.
8	26	Pine wood, 1⅝ inches diameter	None	Excellent	3 years; ok.
9	22	Laminated wood	None	Excellent	3 years; ok.
10	23	Bakelite, later balsa	None	Poor; dilatation not well maintained	1½ years. "Acceptable"
11	23	Bakelite	None	Excellent	2 years; ok.
12	20	Bakelite	None	Excellent	21 months; ok.

In one underdeveloped married white girl of 26 years who had minimal pubic hair and an undeveloped female body form, I enlarged the lead-pencil-sized vagina by slitting the walls longitudinally, stretching the canal to adequate diameter manually, and applying local thin skin grafts. The grafts were tied over a tin cylinder covered with dental molding compound. After four or five days, her body heat softened the molding compound, exposing the edges of the tin tube which gave considerable discomfort. On estrogens this patient is able to menstruate regularly and she says the vagina has functioned satisfactorily for over ten years.

The wooden prostheses are best covered with a rubber sheath and fitted with a screw eye in the lower end, so that they can be tied to a belt at night to maintain the proper position. I have found glass forms and dilators were so often broken that I have abandoned their use.

Cases With Atresia of the Lower Vaginal Canal Only (Table III).—In 4 interesting cases only the lower third of the vagina was found either obstructed or not adequately developed.

TABLE III. PARTIAL AND COMPLETE CONGENITAL ATRESIA OF LOWER THIRD OF VAGINAL CANAL

CASE NO.	AGE	DEFORMITY	RESULT	CHECKUP
13	22	Atresia of lower third with channel	Excellent	3 years; satisfactory. Infected abortion
14	14	Narrow lower third. No menses	Satisfactory	2 menses
15	20	Atresia of lower third. Twenty-day dribbling menses	Excellent	6 years. 1 child, 1 abortion. Coitus satisfactory
16	12	Complete atresia of lower third with hematocolpos with complete ureteral obstruction	Excellent	3 years; satisfactory. Early dilatation required first year

CASE 13.—A girl of 22 years of age who urinated and menstruated through a small opening under the clitoris was the first of the group. An ample introitus was achieved by cutting down on a grooved director inserted in this channel and by sewing the cut edges to the adjacent skin at either side. The patient was followed for three years during which time she was treated at our hospital following an infected induced abortion.

CASE 14.—A fairly well-developed 14-year-old Puerto-Rican when first examined had already had an operation for failure to menstruate which had resulted in the loss of the floor of the middle third of the urethra. By means of a surgical probe, I was able to locate a minute vaginal opening which, when dilated to an adequate size, disclosed an upper vagina of normal capacity. The urethra was reconstructed at the same operation and regular menses followed.

CASE 15.—A twenty-year-old single white girl, whose scant menses lasted for twenty days each month and were accompanied by considerable pain, was found to have a probe-sized sinus tract. Injection of this with Lipiodol revealed that the upper two thirds of the vaginal canal was of normal configuration. It was possible to draw the lower margin of this upper, normal vaginal segment down to the introitus and suture it in that position. The patient has now had normal menses and satisfactory coitus for six years, with one full-term child and one spontaneous abortion.

CASE 16.—A white child of 12, with well-developed breasts and heavy pubic and axillary hair, was found to have a hematocolpos which by direct pressure had blocked off the right ureter. The uterus was easily palpated abdominally, at the summit of the mass above the pubis. Because of a marked spina bifida, she also had incontinence of urine and feces. A simple channel to relieve the accumulation of old blood was first made and then the mucosa of the upper vagina was pulled down and sutured to the skin as in the previous case. Dilatation of the vaginal orifice was required three times during the first year, but menses were occurring normally three years after operation.

TABLE IV. OTHER INTERESTING CASES OF VAGINAL APLASIA OBSERVED

CASE NO.	AGE	DEFORMITY	RESULT	CHECKUP
17	24	Cloaca	Partial partition by operation. Pregnant	Result improved over original status. 2 years, "less fecal spill during coitus"
18	20	No vagina; urethral coitus	Operation to create artificial vagina refused	Satisfied
19	27	Artificial vagina, full-thickness skin grafts; wide, gaping introitus	Unsatisfactory	Acute rectal gonorrhea

A Case With Cloaca.—

The only patient with this anomaly whom I have seen had already been operated upon. A thin partition extended from the vaginal vault to the vicinity of the introitus, but there was no sphincter at this lower end of the rectum, causing considerable fecal incontinence. When seen she was well along in pregnancy and I advised delivery by cesarean section.

Summary and Conclusions

1. The construction of an absent vagina, or the reconstruction of a deficient one, has valuable psychological effects.

2. With a cooperative patient a satisfactory result is obtained in these cases, whether the channel is lined with skin grafts or is allowed to epithelize itself.

3. It is better psychotherapy to avoid the use of grafts, thus leaving no visible scars on the body surface.

4. Except for drainage of a hematocolpos or a hematometra, the procedure should be deferred until adult stature has been attained and marriage has occurred or is imminent.

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Discussion

DR. VIRGIL S. COUNSELLER, Rochester, Minn.—The surgical correction of congenital anomalies is one of the most interesting developments in surgery. A patient with one anomaly is apt to have others in different parts of the body. Only in the last few years have such anomalies of the heart and also tracheoesophageal fistulas been successfully treated by surgical procedures. The high incidence of urinary anomalies associated with vaginal aplasia is well known, so that their presence or absence must be established primarily before correction of the vaginal defect is instituted.

Many methods of correction have been attempted, as detailed by Dr. Barrows. There have been successes and failures in all methods. It should be said that the simplest method of establishing a vaginal tract will give the greatest number of successes. In 1947, I reported 100 cases of this congenital anomaly. Since then we have encountered 40 more. Most patients have been treated by the split-skin graft; occasionally no graft was used at all. By and large, I would say it is far safer to use skin grafts on all of these patients because I have learned it is impossible to determine which patients will develop their own vaginal epithelium and which will not. Skin grafting will always result in some failures; in these cases I have used intestine, since so far I have never been able to make a second skin graft take by any secondary method used for skin grafting.

I would like to enumerate the steps which I consider required for a successful graft: (1) carefully dissect the tract, (2) control bleeding, (3) use absorbable, never nonabsorbable, suture material in the tract, (4) use soft sponge-rubber stent covered with split-skin graft, (5) close the vagina, (6) urge early ambulation, (7) examine rectum every other day to express any sanguineous material from around stent, (8) leave stent in vagina for 3 weeks, (9) open vagina and remove stent, and (10) cleanse new vaginal tract and replace stent with a polyethylene mold; the patient wears the mold for a few days until all soreness is gone, then removes it and replaces it at intervals daily to avoid contraction.

There has been much discussion about contraction of the new skin-covered tract. This contraction will always occur if there is any absence of the graft, that is, contraction occurs when the mold is removed if the graft is faulty.

I have discussed this phase of our troubles with plastic surgeons who are accustomed to making split-skin grafts for repair of tubular structures such as the auditory canal, lacrimal duct, nasal cavity, and pharynx. They advise that if a complete graft can be held in place for 4 to 6 months, there will be no further contraction.

DR. C. GORDON JOHNSON, New Orleans, La.—Fortunately, vaginal aplasia occurs quite rarely, and its successful correction completely changes the unfortunate patient's entire life.

In each instance the chief complaint has been failure to menstruate, at times associated with cyclic abdominal pain. May I emphasize at this time the importance of thorough pelvic examination of all adolescent girls giving such a history. Parents are told, often without an examination, not to worry. These individuals have well-developed feminine characteristics, as the ovaries are not involved in such a malformation.

On the Tulane Gynecological Service we have had experiences similar to those of Dr. Barrows. In one patient a pedicle graft was attempted, but unsuccessfully. Formation of a satisfactory vaginal canal was accomplished after a balsa-wood mold, covered with pinch grafts, was used. In 2 instances an opening was created and a balsa-wood mold was admitted without grafts. Epithelization took place, but required a considerable length of time.

The technique used during the past several years by the Gynecological Department at Tulane University for construction of an artificial vagina is as follows: After a cavity is prepared by blunt dissection of the space between the rectum and the bladder, a balsa-wood mold covered with a split-thickness graft is placed in this area. The skin at the outermost portion of the mold is then sutured with interrupted cotton to the skin edges of the lateral side of the vaginal orifice. This split-thickness graft is usually obtained from the buttocks, in order to prevent the presence of disfiguring scars on the legs or thighs of the individual.

Three balsa-wood molds, which had previously been shellacked in order to make them smooth, are usually prepared. The largest mold, to which a graft has been attached, is inserted first, and allowed to remain in the space created for approximately 10 to 12 days. Under anesthesia this mold is then removed, and replaced by a smaller one, which is then kept in position until skin grafting has taken place successfully. If advisable, after several weeks, a third smaller mold is used. The patient is taught to remove and to insert the mold after douching. Coitus is advisable as soon as evidence of successful grafting is present. We agree with Dr. Barrows that this corrective operative procedure should not be performed unless the patient is married, or plans to be in the near future.

A review of the records from Touro Infirmary in New Orleans discloses the interesting fact that the majority of the patients there were treated by plastic surgeons using a graft applied on a Pyrex form. In most instances it was necessary to repeat the grafting several times, at intervals of 6 to 12 months before a functioning vaginal canal was established. In no instance, however, was abdominal exploration done to determine the condition of the internal generative organs. Such exploration, in our opinion, should usually be done. I should like to ask Dr. Barrows his opinion concerning this.

DR. BARROWS (Closing).—In attempting to form quick pedicle grafts from the thighs in my first case, sloughing of the distal portion on both legs, left too little material to fashion a vagina of adequate depth. For this reason, we turned to the Kirschner-Wagner procedure, which gave me a number of excellent results, with no uncorrectable failures. Our only change in this procedure has been to eliminate the use of skin grafts, by maintaining adequate dilatation.

I have had no personal experience with the Baldwin operation, but have observed two patients so treated, who have had continuous severe irritation of the vulva and surrounding areas from the profuse secretion from the lining intestinal mucosa.

I am very much in favor of exploratory laparotomy carried out under the observation of the operator who is to create the artificial vagina. At present, we are doing both procedures simultaneously, by using a double operating team. This, of course, follows a careful radiological study of the entire urinary tract.

INTRAUTERINE RADIUM FOR DYSFUNCTIONAL BLEEDING*

A Long-Term Follow-up Study

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IN 1933, Keene and Payne[1] reported "The Results of Radium Treatment in Functional Uterine Bleeding." That report was based upon a follow-up study of 391 patients who were treated by this means prior to 1931. The present study concerns the long-term results of radium therapy upon 290 of those patients as to the control of bleeding, the need for subsequent pelvic surgery, the maintenance of procreative function in the younger groups, and the development of malignancy following the radiation.

Table I shows the original age grouping in decades with the radium dosage in milligram hours and a similar grouping of the patients upon whom data were obtained for the present analysis. For the entire series the long-term absolute follow-up reached 74 per cent. During the interval between the original follow-up and the present one 51 patients died of nonmalignant unrelated disease, to leave a residuum of 340 patients, of whom 290 (86 per cent) were followed for a period of 25 or more years. In general the radium dosage increased as the age advanced, with none receiving more than 300 mg. hr. in the youngest category, and none receiving less than 500 mg. hr. in the oldest group. The customary dosage at that time approximated the equivalent of ten times the age of the patient as expressed in milligram hours. The usual technique of the radium application consisted of the intrauterine placement of 50 mg. of radium salt with 1 mm. of platinum and 2 mm. of rubber filtration in the manner described by Clark and Norris.[2] As to the follow-up it was impossible to obtain more information from the younger age groups. This is unfortunate, for they proved to be most interesting as the analysis progressed.

TABLE I. FOLLOW-UP 1931 TO 1955

AGE GROUP	ORIGINAL NUMBER	NUMBER FOLLOWED	RADIUM DOSAGE (MG. HR.)				
			100 TO 300	300 TO 500	500 TO 1000	1000 TO 2000	2000 TO 2400
14 to 20	21	14	14	0	0	0	0
20 to 30	84	49	40	7	2	0	0
30 to 40	91	70	4	32	23	10	1
40 to 50	165	132	2	14	69	44	3
50 to 60	30	25	0	0	10	14	1
Total	391	290	60	53	104	68	5

In the original study the control of bleeding by the initial treatment is shown in Table II to range from 53 per cent in the youngest to 92 per cent in

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the oldest group. Reradiation of the uncontrolled cases resulted in improved results in the order of 88 to 100 per cent. For the present analysis, inquiry as to the control of bleeding brought replies at great variance with those of the original report, to range from 49 per cent success in the youngest to 92 per cent in the oldest group. This discrepancy may be explained in one or all of several ways. The recent inquiry did not detail the effect of subsequent treatments; the memory of the younger patients, most of whom received a submenopausal dose with resumption of menstruation, may be faulty; the length of the present follow-up may have permitted more recent menstrual aberrations to alter the picture of the therapeutic result.

TABLE II. RESULTS AS TO CONTROL OF BLEEDING

AGE AT TREATMENT	BLEEDING CONTROLLED (PERCENTAGE)		
	ORIGINAL REPORT		
YEARS	FIRST RESULT	FINAL RESULT	PRESENT STUDY
14 to 20	53	88	64
20 to 30	70	88	49
30 to 40	90	95	70
40 to 50	92	99	91
50 to 60	92	100	92

The subsequent pelvic operations, including the reapplications of radium, are listed in Table III. In general their greatest incidence occurred in the younger age groups and consisted of repeat curettements and of repeat radium applications. Indeed three of the curettages and seven of the radium applications for benign bleeding were repeated twice at intervals varying from one to ten years following the original effort. Eleven procedures were conducted for complications of pregnancy: 8 evacuations following abortion and 3 cesarean sections. The miscellaneous operations consisted of 11 plastic repairs and 2 instances of ovarian surgery. The subsequent hysterectomies, numbering 30, proved to be the most interesting group. The time interval between the radiation and the hysterectomy with the indication for this procedure is shown in Table IV. Twenty-two of the 30 hysterectomies were done from 10 to 30 years following the radium, thereby leaving this expanse of time for possible utilization of the uterus. Four operations were done for persistent dysfunctional bleeding, despite the reapplication of submenopausal doses of radium. The largest number, about one half, were necessitated by the subsequent manifestation of uterine myomas. So many of these had failed to respond to reradiation in small dosage that we grew to suspect the overt presence of myomas when ordinary radiation failed to control apparent dysfunctional uterine bleeding. The 5 operations for corpus cancer will be considered in the discussion of subsequent malignancy. Seven miscellaneous indications for operation consisted of: uterine disease, 3 (prolapse, dysmenorrhea, adenomyosis); ovarian disease, 2 (bilateral cysts, cancer); and pregnancy complications, 2 (deciduitis and cesarean hysterectomy). Nineteen pregnancies occurred prior to the hysterectomies, 2 of which preceded the development of corpus cancer in one patient.

Details of the 19 pregnancies, which were distributed among 10 of the patients, appear in Table V. None occurred in the 4 instances of persistent dysfunctional bleeding, to suggest failure of the submenopausal radiation to alter defective ovulation. For the group with myomas, 13 pregnancies resulted in 6 miscarriages, one stillbirth, 6 normal children, with 2 grandchildren. The 2 conceptions preceding the corpus cancer terminated in normal children, who were born six and seven years following the radium application. This patient

received 300 mg. of radium at the age of 19 for dysfunctional bleeding associated with endometrial hyperplasia and the corpus cancer developed 22 years after the radiation. This interesting development raises several questions: Did the 300 mg. hr. of radium correct the anovulatory cycles and permit pregnancy, to be followed by reversion to the original endocrine status and subsequent malignant endometrial changes? Is it conceivable that radiation could cause the development of endometrial cancer twenty-two years later with two intervening full-term pregnancies? Of the 30 patients who required hysterectomy following radiation, 8 children and 2 grandchildren were born. Obviously this could not have occurred had the initial definitive therapeutic effort been removal of the uterus.

TABLE III. SUBSEQUENT OPERATIONS

Dilatation and curettage	7
Dilatation and curettage and polypectomy	4
Dilatation and curettage and radium (benign)	30
Dilatation and curettage and radium (malignant)	2
Dilatation and evacuation	8
Cesarean section	3
Hysterectomy	30
Myomectomy	1
Miscellaneous	13

TABLE IV. SUBSEQUENT HYSTERECTOMIES

INDICATION FOR OPERATION	NUMBER	YEARS BETWEEN RADIUM AND OPERATION					INTERM PREGNANCIES
		LESS THAN 1	1 TO 5	5 TO 10	10 TO 20	20 TO 30	
Dysfunctional bleeding	4	0	1	0	3	0	None
Uterine myomas	14	1	0	1	4	8	13
Corpus carcinoma	5	0	1	0	2	2	2
Miscellaneous	7	1	2	1	2	1	4
Total	30	2	4	2	11	11	19

TABLE V. POSTRADIATION HYSTERECTOMIES, INTERIM PREGNANCIES

INDICATION FOR HYSTERECTOMY	NO. OF PATIENTS	BECAME PREGNANT	NO. OF PREGNANCIES	OUTCOME		
				MISCARRIAGE	STILLBIRTH	NORMAL CHILD
Dysfunctional bleeding	4	0	0	0	0	0
Myomas	14	5	13	6	1	6*
Corpus cancer	5	1	2	0	0	2
Miscellaneous	7	4	4	2	2	0
Total	30	10	19	8	3	8

*Two grandchildren.

In addition to these patients, 16 others conceived following radiation. Table VI shows the pregnancy potential and achievement for the entire series of 290 patients. The pregnancy potential of 127 patients consists of 102 who were married and less than 40 years of age at the time of radiation, plus 25 who were married subsequent to the radiation before they reached the age of 40. Of this number, 26 (21 per cent) conceived one or more times with a total of 50 pregnancies.

TABLE VI. MARITAL STATUS AT TIME OF AND SUBSEQUENT TO RADIUM

Married—under 40 at that time	102
Subsequently married under 40 years	25
Pregnancy Potential	127
Patients who conceived	26
Number of pregnancies	50

The grouping of the patients by age decade at the time of radiation and the terminations of the pregnancies are shown in Table VII. While the radium dosage does not appear in this table, detailed analysis disclosed no relationship between this dosage and the success or failure of the pregnancies. Of the 50 conceptions, 25 ended in miscarriages, 6 in stillbirths, and 19 in living babies, with 15 subsequent grandchildren. The incidence of both miscarriage and stillbirth is exceedingly high. The former is accounted for largely by 5 patients all of whom, at less than 30 years of age, received less than 350 mg. hr. of radium and each of whom had from two to three abortions with no full-term pregnancies following the radiation. This may be a reflection of the procreative inadequacy that is so frequently seen in dysfunctional bleeding, even though subsequent pregnancy may occur. Of the stillbirths, in only one case was there a history of mechanical obstetrical difficulty, namely, a transverse lie with a contraction ring that required cesarean hysterectomy. This was not done in our hospital. Three were macerated infants at 7 to 9 months; in 2 of these cases the membranes had been ruptured for some time prior to labor. In general, the younger the patients the higher the percentage of normal babies, to suggest better subsequent postradiation development of functional integrity in the early age groups.

TABLE VII. SUBSEQUENT PREGNANCIES

AGE GROUP	NO. PATIENTS	NO. PREGNANCIES	MISCARRIAGES	STILLBIRTHS	LIVE BABIES	GRANDCHILDREN
14 to 20	8	20	8	2	10	3
20 to 30	11	23	15	2	6	9
30 to 40	7	7	2	2	3	3
Total	26	50	25	6	19	15

The condition of the offspring in relation to the age grouping, the radium dosage, and the interval between the radiation and the first pregnancy appear in Table VIII. The dosage consisted of 200 to 500 mg. hr. for all except one patient. She at 31 years received 750 mg. hr., had a normal infant three years later, and that child now has 2 healthy children of 6 and 8 years. The interval between radiation and conception ranged from one to ten years, with the longest average interval in the first age group. Of the 19 pregnancies, 10 occurred in the group that was youngest at the time of the radiation, 6 in the next, and 3 in the 30 to 40 year group; the first generation column is comprised of these. In this generation 2 congenital defects were reported, one case of fatal heart disease and one so-called "blue baby." The mother of the former received 300 mg. hr. of radium two and one-half years prior to the birth of the infant, who succumbed at the age of 9 hours. The "blue baby" recovered, is now 22 years old, and has given birth to 2 healthy infants with no medical or obstetrical difficulty. Of the 15 second-generation children, one died of congenital heart disease at 6 weeks, and 9 are more than 4 years old with no sign of physical, neurological, or mental disturbance. The remaining 5 range from 6 to 24 months in age. All are normal, both in appearance and upon careful physical examination.

TABLE VIII. CHILDREN AND GRANDCHILDREN

AGE GROUP	DOSAGE (MG. HR.)	INTERVAL (YEARS)	FIRST GENERATION		SECOND GENERATION	
			INFANTS	DEFECTS	INFANTS	DEFECTS
14 to 20	2-300	3 to 10	10	0	3	1
20 to 30	3-500	1 to 7	6	1	9	0
30 to 40	3-750	1 to 3	3	1	3	0
Total offspring			19	2	15	1

The development of pelvic malignancy following radiation has been the subject of much discussion and much retrospective reasoning. In a forward-view effort, Turnbull[3] summarized the literature to collect 4,539 instances of radiation for benign bleeding with the following incidence of subsequent pelvic carcinoma: cervix—0.22 per cent; corpus—0.79 per cent; ovary—0.15 per cent. The duration of the follow-up ranged from three months to twenty-five years. He also reported 739 additional instances of radiation, with a follow-up of six to sixteen years, during which the occurrence of pelvic cancer was: cervix—0.8 per cent; corpus—0.54 per cent; ovary—0 per cent. In the present series of 290 patients who have been followed twenty-five years or more, 24 malignancies have developed, 10 of which were nongenital (Table IX). Of the genital malignancies 2 (0.7 per cent) were cervical, 6 (2.1 per cent) were corporeal, one (0.35 per cent) was ovarian, and 5 (1.7 per cent) were mammary in origin. Five of the patients who developed corpus cancer were less than 40 years of age when treated by radium for dysfunctional bleeding. Although 25 were older than 50 at the time of radiation, which varied from 500 to 2,400 mg. hr., no pelvic cancer developed in this subgroup. The endometrium at the time of the preliminary curettage showed extensive hyperplasia in 12 instances; 9 were classified as normal, 3 as insufficient tissue for diagnosis, and one as endometritis. The lack of subsequent carcinoma in this small group is reassuring in the light of Turnbull's recent recommendation that patients of 50 years or more with endometrial hyperplasia should be subjected to hysterectomy because of the danger that corpus cancer may follow radiation for benign bleeding.

TABLE IX. SUBSEQUENT CARCINOMA

AGE AT TREATMENT	NO. PATIENTS	TOTAL MALIGNANCIES	GENITAL SYSTEM				OTHER SITES
			CERVIX	CORPUS	OVARY	BREAST	
14 to 20	14	1	0	1	0	0	0
20 to 30	49	4	0	2	0	1	1 Rectum
30 to 40	70	5	0	2	0	2	1 Colon
40 to 50	132	9	2	1	1	1	4 Neck, lung, kidney, rectum
50 to 60	25	5	0	0	0	1	4 Colon, rectum, stomach, gall bladder
Total	290	24	2	6	1	5	10

Table X summarizes the instances of pelvic carcinoma as to the patient's age, the endometrial condition at the time of treatment, the dosage, the interval between the radium application and the diagnosis of cancer, and the eventual outcome. Despite the fact that only 133 patients were less than 40 years of age against 157 who were over 40 at the time of radiation, five of the corpus cancers developed in the younger group. Of additional interest is the endometrial picture of hyperplasia in 3 of the 5 patients who were less than 40 years of age. The radium dosage varied from 300 to 1,200 mg. hr. and the interval between the radiation and the cancer ranged from three to twenty-four years. One patient developed corpus cancer at the age of 24, three years after 300 mg. hr. of radium, while another, after 1,200 mg. hr., gave evidence of malignancy in four years. These short intervals may raise the question as to the presence of early carcinoma at the time of the original treatment. The paraffin blocks and the microscopic slides were rechecked recently with this in mind and no evidence of malignancy was present. One patient received 300 mg. hr. of radium at 19, had one baby at 25 and another at 29, and developed carcinoma of the corpus at 41 years of age. Did the radiation correct the ovarian dysfunction long enough to permit two pregnancies and then

after twenty-two years incite malignant endometrial transformation? Or was some obscure endocrine aberration temporarily suspended to recur later with stimulation of corpus cancer? The single instance of ovarian carcinoma is tragic: 400 mg. hr. of radium at 40 years, therapeutic abortion at 44 because of otosclerosis, and death from ovarian malignancy at 51. Most certainly this patient would have profited by a hysterectomy and bilateral salpingo-oophorectomy at the time of the radiation, but how many of us would have been so radical?

TABLE X. SUBSEQUENT CARCINOMA, PELVIC ORGANS

AGE AT TREATMENT	DOSAGE (MG. HR.)	ORIGINAL ENDOMETRIUM	INTERVAL (YEARS)	OUTCOME	COMMENT
Cervix.—					
43	500 600	Normal Insufficient tissue	17	Death	Sarcoma of cervix
47	1,200	Normal	24	Living and well	Radiation, 1950
Corpus.—					
19	300	Hyperplasia	22	Living and well	Two babies 6 and 10 years post radium
21	300	Hyperplasia	3	Living and well	Married. No pregnancy
21	400	Hyperplasia	14	Living and well	Not married
30	925	No record	10	Living and well	Married. No pregnancy
32	1,200	Proliferative	4	Death	Married. No pregnancy
47	750	Proliferative	24	Living and well	Para iii before radium
Ovary.—					
40	600	Hyperplasia	11	Death	Therapeutic abortion 4 years post radium

Since the breast is considered to be a genital structure by many, Table XI is included. Three of the 5 patients who developed breast carcinoma required more than one application of radium to control the dysfunctional bleeding. This may suggest hormone inbalance, to eventuate in breast cancer, or the repeated submenopausal dosage may have stimulated perverted ovarian function to lead eventually to mammary carcinoma.

TABLE XI. SUBSEQUENT CARCINOMA OF BREAST

AGE AT TREATMENT	DOSAGE (MG. HR.)	DATES	ORIGINAL ENDOMETRIUM	INTERVAL (YEARS)	OUTCOME
23	125 400 700	1923 1924 1925	Proliferative	28	Living and well
38	600 600	1924 1927	Secundines Proliferative	22	Death
39	400	1933	Secretory	4	Living and well
45	1,200 600	1919 1925	No report	19	Living and well
52	600	1928	Proliferative	14	Death

The question of whether or not the incidence of cancer in all sites, particularly the genital system and most particularly in the uterine corpus, is increased by previous radiation has not been answered nor will this study furnish the answer. Table XII is a nonstatistical unscientific comparison between the subsequent cancer development in this study and the cancer expectancy

as indicated in Randall's[4] tables. Obviously this comparison is not valid in many respects, chief of which are the small number of cases in the present series and the fact that many of these patients may develop cancer later as they advance in years. However, the Randall expectancy figures at 20 and 60 years of age, for all sites and for the cervix, the corpus, the ovaries, and the breasts, exceed the range of occurrence in the present study for each category except that of the uterine corpus. For this organ our cancer incidence is almost twice the highest probability figure in the Randall table. This may suggest that the material in this study possessed some obscure quality that predisposed to corpus cancer or that the intrauterine radium did in certain instances stimulate subsequent malignant transformation. While this finding is suggestive, no statistical significance is claimed. If this series of patients is followed consistently for the next twenty-five years, our successors may come closer to the answer.

TABLE XII. SUBSEQUENT CARCINOMA OF GENITAL SYSTEM
APPROXIMATE COMPARISON WITH RANDALL'S EXPECTANCY TABLE

RANGE AND INCIDENCE	ALL SITES (%)	CERVIX (%)	CORPUS (%)	OVARY (%)	BREAST (%)
Randall range at 20 and 60 years	23.8 to 18.7	2.3 to 1.1	1.6 to 1.1	1.0 to 0.6	5.3 to 3.9
Present series, range from highest to lowest	7.1 to 3.8	1.5 to 0.0	7.1 to 0.0	0.8 to 0.0	4.2 to 0.0
Present series, incidence, all ages	8.0	0.7	2.1	0.3	1.7

Summary

In a long-term follow-up study of 290 patients who received intrauterine radium for dysfunctional uterine bleeding, the following significant developments were noted:

The control of bleeding was reported to have been considerably less than the original study indicated. This was especially true for the younger age groups who received submenopausal doses of radium.

In the younger groups subsequent relevant surgery consisted largely of repeat curettages, at times with repeat radium applications; operations for complications of pregnancy; and hysterectomies for either intractable dysfunctional bleeding or the interim appearance of myomas.

For the entire series 50 pregnancies followed the radium applications, with 19 living babies and 15 subsequent grandchildren. Of the former, one died of congenital heart disease at 9 hours and the remainder are normal. Of the latter, one died of congenital heart disease at 6 weeks and the remainder appear to be normal in every respect.

Twenty-four malignancies developed following the original radiation, 10 of which were not genital in origin. Of the remaining 14, 2 were cervical, 6 were corporeal, one was ovarian, and 5 were mammary. Nonstatistical comparison of this incidence of malignancy with the Randall expectancy table shows it to be lower in every category except that of carcinoma of the corpus. Here it is almost twice as high.

Conclusions

Submenopausal intrauterine radium dosage is moderately effective in the control of intractable dysfunctional bleeding in the younger age groups and menopausal dosage is definitely so in the older groups. The incidence of subsequent procreative capability with normal children and normal grandchildren outweighs the occasional need for later definitive pelvic surgery. The danger of subsequent pelvic malignancy does not outweigh the advantages of radiation for benign bleeding except possibly in the case of corpus cancer. Similar studies to the present one and continued observation of the material in this study may prove whether or not an increased incidence of corpus cancer follows radiation for benign uterine bleeding.

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Discussion

DR. FRANK R. SMITH, New York, N. Y.—The authors have approached this study from four important angles: (1) control of bleeding; (2) need for subsequent pelvic surgery; (3) subsequent pregnancies; and (4) development of malignancy following the irradiation.

1. Control of Bleeding.—The disparity between the results in the younger group as compared with the older group is not surprising in view of the greater capacity for recovery and the smaller doses of radium received by the younger group. Certainly the opportunity was given to those under 30 years of age to recover their ovarian function, which was denied to those over 50 years of age.

2. Subsequent Pelvic Surgery Including Reirradiation.—Of the 290 patients studied, 98 (33.7 per cent) required some form of further treatment. While not entirely comparable, it is of interest to note that of some 600 patients with menopausal bleeding whom we treated with curettage alone, less than 40 per cent required further therapy. Of this group, however, 10 per cent showed carcinoma of the endometrium and about 5 per cent had carcinoma of the endocervix. Table III shows that 30 patients were reirradiated. While the predominant age group is not stated, I suspect they are mostly the younger women. Of 30 patients who required hysterectomy, 14, or nearly half, had fibroids.

3. Subsequent Pregnancies.—Isolated unusual cases tend to make exaggerated impressions. For example, a 36-year-old patient, treated by Dr. W. P. Healy with 1,800 mg. hr. of radium for uterine bleeding associated with a fibroid uterus, conceived eight months later and again four years later. Both children are alive and normal today, 18 and 22 years of age. However, in this study, with a possibility of pregnancy in 127 patients, only 26 conceived, and of the 50 resulting pregnancies, 25, or one half, resulted in miscarriages and 6 in stillbirths. Of the 19 living children, all but 3 were borne by women under 30 years of age. The incidence of congenital cardiac defects was high. From the record, radium therapy for benign bleeding hardly seems to improve fertility in young women even if administered in small doses. Myomectomy seems to be the method of choice.

4. Development of Malignancy Following Irradiation.—With our present knowledge there is no evidence to show that irradiation for benign uterine bleeding influences extragenital neoplasms. The incidence of corpus cancer after irradiation is the important item and

is difficult to evaluate. Even comparison with the reported incidence per 100,000 population would not be accurate because these women studied all had some pelvic pathology. At Memorial Hospital 752 patients were treated from 1920 to 1930 with intrauterine radium for benign uterine bleeding. Seven of these developed cancer of the endometrium ten or more years later. Difference of criteria used makes comparison of results of clinics of doubtful value. Our criteria were that ten years must have elapsed between irradiation and appearance of the cancer and review of curettings at the time of irradiation must prove them benign. On time alone, we would have had 24 patients to report.

I agree with Dr. Payne that the danger of subsequent pelvic malignancy does not outweigh the advantage of radiation for benign uterine bleeding, but I would limit irradiation for benign lesions to menopausal bleeding without active fibroids.

DR. A. N. ARNESON, St. Louis, Mo.—The principal deterrents to the use of radiation in the treatment of benign uterine bleeding are risk of subsequent cancer in the endometrium, and in younger women the risk of injury to conception with potential mutations, and the possibility of permanent amenorrhea. Upon an empirical basis we know with reasonable assurance that certain dose levels will usually permit reappearance of menstruation. It is very difficult, however, to assess the risk of cancer or genetic effects.

I have little personal experience with the use of radiation in benign bleeding, but it must be admitted that I have been more deterred by the fear of genetic effects than by fear of endometrial cancer. In conjunction with Dr. Smith's comment upon corpus cancer following treatment for cervical lesions, I have known of only one such instance. Specific genetic effects are far more difficult to recognize. Mutations may be hidden, and they may not be apparent for several generations. Some geneticists contend that approximately 1 of every 5 extinctions is the result of mutations, and suspect that the rate may be doubled by gonadal irradiations of less than 100 r. The two instances of congenital heart disease in Dr. Payne's series are not proved to be mutations, but they cannot be set aside as being free from genetic effects. Follow-up into the third generation is one of the important contributions of Dr. Payne's report. There are masses of laboratory data, but there are few data upon humans.

A point of discussion with particular appeal to me is in reference to the somewhat provocative speculation upon what effect, if any, direct action upon endometrium has in the radiation control of benign uterine bleeding. It is generally agreed that any favorable response is due to changes induced in the ovaries. We do not, however, know the part played by an endometrial effect in the correction of abnormal bleeding, nor in the production of temporary amenorrhea. Dr. Payne reports more effective control in older patients. That is found in his original report, among those retreated for initial failure, and in the current study. The greater dose those patients received is apparently responsible for that difference.

Physiologic repair may vary in different tissues and at different ages. Full recovery may return conditions to the original circumstances primarily responsible for abnormal bleeding. Incomplete repair may remove the stimulus responsible for clinical symptoms, or render the endometrium incapable of responding abnormally. We can discard the possibility of a stimulatory action of radiation.

Evidence of an apparent difference in promptness of radiation injury to endometrium and to ovary can be found in the onset of menopausal symptoms in young women irradiated for cervix cancer. Vasomotor symptoms may not appear for several weeks after the beginning of treatment, at which time the endometrium may be markedly degenerated. That delay in menopause symptoms is in sharp contrast with the usual experience following oophorectomy.

Evidence that endometrial changes proceed more rapidly than changes in ovarian function was noted also by Sherman, Nolan, and Allen in assessing experimentally the tissue effects from radioactive gold. One horn of the uterus in rabbits was injected with

radioactive gold, and the animal given an injection of gonadotropin at the same time. Tissue changes were studied by biopsy at laparotomy performed one week later, and by repeat operation or sacrifice of the animal following a second gonadotropic stimulation 4 or 5 weeks later. On the untreated side the ovary responded normally with progestational effects in the endometrium of the adjacent horn following each injection of gonadotropin. On the exposed side the endometrium failed to show any progestational effect, but the ovary often showed follicle stimulation at one week.

It is interesting to note that other authors have conceived the idea of utilizing a pure beta emitter within the uterus with a minimum of ovarian exposure. I suspect local endometrial effects to be important, and urge Dr. Payne and his collaborators to continue their study with that possibility in mind. They have an amazing opportunity for long-term follow-up study. They may have experienced a sense of disappointment at failure to solve certain pertinent questions regarding sequelae of treatment. That should not be, however, because they have contributed useful biological data. It is not unrealistic to assume that the contribution of researches in biology will equal the significance of earlier physical researches in our knowledge of radiotherapy.

DR. WALTER T. DANNREUTHER, New York, N. Y.—In October, 1932, I published a paper reviewing the end results in 109 patients in a ten-year period in whom I had used intrauterine radium therapy as a conservative method of treatment. The ages of these patients, 20 to 60 years, closely paralleled Dr. Payne's. So did the technique and dosage, except that most of my younger patients were given a slightly higher dosage.

The radium was used for single fibroid tumors characterized by bleeding only and no larger than a three months' pregnancy; for adolescent and menopausal bleeding and adenomyosis, when all possibilities of medical treatment had been exhausted, curettings revealed nothing of significance, and no pathological alterations in the pelvis could be detected; for recurrent bleeding due to "swiss-cheese" hyperplasia after previous curettage; for cellular changes in the cervix which the pathologist refused to diagnose as definite carcinoma; for profuse bleeding from tuberculosis of the endometrium; and for sterilization for hyperthyroidism after a previous thyroidectomy, and after devastating cardiac decompensation in a previous pregnancy from which the patients emerged as cardiac cripples. As a result of this experience I concluded that radium therapy is well adapted to a small select group of fibroid tumors, that it is an excellent substitute for hysterectomy in cases of adenomyosis, recurrent endometrial hyperplasia, and menopausal bleeding, and for bleeding from a tuberculous uterus.

I learned that the menstrual function will be preserved in 78 per cent of cases when the dosage is 750 mg. hr. or less and that many of these women may have normal babies. I also found that radium therapy has a depressing effect on sexual inclinations in 13 per cent of cases, but on the other hand it sometimes increases them.

Since 1932 I have utilized radium therapy in an additional 326 cases, for practically the same indications, with equally satisfactory results. I am embarrassed by the fact that I did not have time before this meeting to document this discussion, but I can say that in these 435 personal cases in 35 years, there were but two instances of subsequent malignancy of the uterus, both in the corpus.

I think that I had less occasion to repeat the treatment itself than Dr. Payne did, probably because I used slightly larger initial doses. There is no doubt that a certain percentage of these patients would otherwise have been subjected to hysterectomy, and had certain people seen some of the specimens, we both would probably have been accused of participating in the hysterectomy racket. I do not believe that the rare instance of uterine malignancy developing years after a radium application for a benign lesion is sufficient reason to abandon this conservative method of treatment completely, as some others have recently advocated.

DR. WILLIAM STUDDIFORD, JR., New York, N. Y.—Twenty-two years ago a young girl 14 years old was admitted to Bellevue Hospital for prolonged uterine hemorrhage. During the next five years this young lady was repeatedly admitted to the service for the same complaint and treated with curettage and transfusions. A review of these sections shows a normal proliferative endometrium in all specimens.

At the age of 20 her menstrual cycles became normal and continued to be normal up until about eighteen months ago. Last year she was readmitted to the hospital because of recurrent prolonged uterine bleeding. Curettage showed that she had carcinoma of the corpus which resulted in total hysterectomy. I mention this case because here is a young woman with the background of Dr. Payne's young patients, who developed carcinoma of the corpus at a very early age without any irradiation treatment at all.

DR. WILLARD M. ALLEN, St. Louis, Mo.—Some work we did a few years ago, dealing with the effects of irradiation on the endometrium of the rabbit, has some bearing on the effects of irradiation on the human uterus. The rabbit is a convenient animal to use for three reasons: the uterus is large enough to be convenient, the uterus is bicornuate so that one horn can be irradiated and the other horn used as a control, and finally the stimulating effects of the steroids are well understood.

In the rabbit progesterone produces a cytological alteration of the endometrium which is called the progestational change and which is akin to the premenstrual change in the human endometrium. The primary experiments which we did were carried out as follows: ovulation was induced in rabbits with chorionic gonadotropin and the following day radioactive gold was introduced into one horn of the uterus, and then the animals were sacrificed on the seventh day after ovulation and the uterus and ovaries subjected to microscopic examination. The ovary on the opposite side from the gold contained corpora lutea and the endometrium of the opposite horn showed full progestational change. This indicates that the corpora lutea were producing progesterone and that the essentially unirradiated horn was responding normally to the progesterone. The irradiated horn, on the other hand, showed no progestational change, indicating that progesterone was unable actually to stimulate the normal proliferative changes while the endometrium was being irradiated by the radiogold.

In a second type of experiment, one horn was irradiated with gold and a month later the endometrium was subjected to the stimulating effects of progesterone. In this experiment too the irradiated horn did not show any progestational change whereas the nonirradiated horn responded normally to progesterone.

These two experiments indicate that irradiation interferes immediately with the effects of progesterone on the epithelial cells of the endometrium, and also that the alteration of these cells persists for some time following the irradiation. These preliminary studies were of such interest that we are now studying more thoroughly the effects of less than lethal amounts of irradiation on the epithelial cells and the stromal cells of the endometrium. It seems to me that these observations in animals may have some significance in interpreting the low incidence of pregnancy and the high abortion rate in the cases reported by Dr. Payne.

DR. PAYNE (Closing).—The development of other reasonably effective and safe therapeutic measures has decreased the frequency with which intrauterine radium is needed for benign bleeding. However, the occasional instance occurs when it is needed and, unless more conclusive evidence should come forth to contraindicate its use, it should not be banished from our therapeutic armamentarium.

AN EVALUATION OF SUPERVOLTAGE IRRADIATION THERAPY IN THE TREATMENT OF PELVIC MALIGNANCY*

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THE purpose of irradiation therapy in gynecologic malignancy is the elimination of the cancer without untoward injury to the normal tissues. Various types of irradiation are available including radiation isotopes, such as Co^{60}, radium used as local sources or as teleradium therapy, medium voltage x-ray therapy (200,000-250,000 volts), supervoltage therapy (1 to 3 million volt range) and the higher voltages produced by the cyclotron and the betatron.

Since 1949 a 2 Mev Van de Graaff x-ray generator has been in clinical use at the American Oncologic Hospital. This type of machine is energized by static electricity and depends upon the carrying of an electric charge which is sprayed on a moving insulated rubber belt at about 35,000 volts from a rectified current. This charge is carried to an insulated metal dome and then is distributed to a number of surfaces equal in potential, each connected to sections of the x-ray tube. Each of these surfaces has a charge of about 65,000 volts. This generator, which is stationary, produces an approximately constant potential.

The American Oncologic Hospital is a 58-bed institution which deals primarily with patients who have neoplastic disease. Very few of the patients come of their own accord to the hospital. The majority of the patients are sent by physicians or other hospitals when a diagnosis of carcinoma is made or is suspected.

Originally it had been hoped that it would be possible to treat alternate patients by means of supervoltage irradiation and the usual 200,000-250,000 volt therapy. However, because of the referral of many patients in whom supervoltage therapy seemed to offer definite advantages over conventional medium-voltage therapy, it has not been possible to follow this plan. Many of the patients seen were considered to be treatment failures elsewhere and were sent to the hospital for the consideration of 2 million volt treatment as a last resort.

Material

This report considers all patients with histologically proved malignancy, primary in the female genital organs, treated by means of supervoltage therapy from Jan. 1, 1949, to July 1, 1956.

*Presented at the Sixty-seventh Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Va., Sept. 6 to 8, 1956.

There are 126 patients whose records have been appraised. Eighty-nine patients had primary malignancy of the cervix, 18 had endometrial lesions, 15 ovarian, and there were 2 patients with carcinoma of the vulva and 2 with carcinoma of the vagina.

Every patient on admission to the clinic or hospital had a complete history and physical examination. In most instances a chest x-ray, cystoscopy, sigmoidoscopy, and barium enema were done as part of the usual preirradiation study. Any deficiency in nutrition was rectified and blood loss was replaced by transfusions and the use of hematinics, either oral or parenteral. Associated infection was controlled by means of appropriate antibiotic therapy; often the broad spectrum drugs were utilized.

The term "palliation" is employed here to denote relief of symptoms. Symptoms varied from excessive vaginal bleeding to edema of the lower extremities, pain, and/or swelling of the abdomen. "Palliation" does not refer to the length of life of the patient concerned since in many instances the patient may have survived for periods of sixteen to eighteen months longer, before death occurred.

The length of time of survival in all cases was longer than the period of palliation.

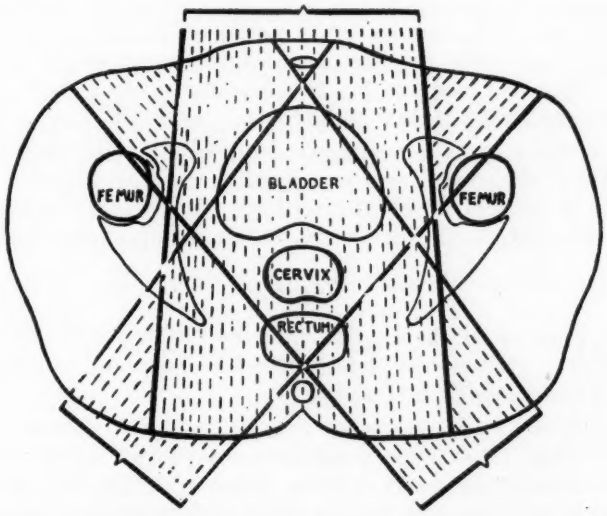

Fig. 1.—Schematic diagram illustrating the portals of entry for supervoltage therapy used in treating cervical malignancy.

Technique

Factors of treatment are 2.00 megavolts, 200 Ma., 70 cm. target skin distance, inherent filter 7 mm. lead, the output somewhat variable, but averaging 60 r per minute.

Daily treatments are usually 300 r per field, the fields being alternated daily. The direction, size, and position of the fields vary with the patients and the primary site of the tumor. In general in disease of the cervix, three portals of entry are utilized, one large anterior portal usually 18 by 15 cm. in size with an average portal size of 180 to 200 cm.^{2} In most instances the beam is directed perpendicularly into the tumor bed; occasionally it is angled 10 degrees caudad. In conjunction with this, two posterior portals are used, angled 20 to 35 degrees medially, usually 15 by 16 cm. in diameter. The gluteal cleft may be shielded by lead and the legs are usually rotated externally.

The schematic diagram demonstrates the usual method by which x-ray therapy is administered in patients with carcinoma of the cervix.

In obese patients the Trendelenburg position is used so that the heavy panniculus may be out of the field and the possibility of intestinal injury is minimized.

Patients with endometrial cancer are treated in a similar fashion, sometimes larger fields being used with the direction altered to suit the case.

Patients with ovarian disease are managed by the use of a greater number of portals, usually six to eight in number.

Vulva

Malignancy of the vulva is best treated by a planned radical type of surgical approach.[1] Exceptionally, there may be cases of vulvar malignancy which may be suitable for irradiation treatment. In this series there were 2 such cases. One patient had had complete, planned, adequate surgical excisional treatment. Six years after her initial treatment, she returned to the Oncologic Hospital; she had not been seen for an interval of fourteen months despite attempted follow-up. On examination she was found to have an extensive recurrent lesion involving the lateral and posterior vaginal walls and the rectovaginal septum. By means of a perineal crossfire, producing an estimated depth dose* of 3,894 r, there was clinical regression of the disease and at the present time, one year later, there is no evidence of active neoplastic disease; the expected postradiation fibrosis is present.

The other patient was an elderly individual with extensive ulcerative vulvar malignancy involving the suprapubic and groin area. Supervoltage x-ray was given to a total of 2,200 r without appreciable change in the lesion. Treatment was discontinued and the patient subsequently died.

Vagina

Primary carcinoma of the vagina may be treated by means of irradiation or radical surgery. There were 2 patients who received supervoltage therapy for this lesion at the Oncologic Hospital.

The first patient had extensive disease and by means of supervoltage therapy a tissue dose of 6,100 r produced complete clinical regression of the neoplasm. The tumor recurred within three months, however, and the patient subsequently was treated by complete pelvic exenteration.

The other patient had previously received adequate therapy by means of radium and external irradiation at another institution with recurrence of the primary vaginal carcinoma within six months. By means of supervoltage therapy an estimated tumor dose of 6,325 r was given with little or no change in the patient's disease.

Ovary

At the American Oncologic Hospital, the preferred management of primary ovarian malignancy is by radical excisional surgery followed by irradiation therapy. As shown in Table I, there were 15 patients with primary ovarian malignancy who received supervoltage therapy. Two patients had been operated upon but clinically there was evidence of probable extension beyond the operative field. These patients received 2 million volt therapy with the use of multiple fields and an estimated tumor dose of 5,000 r. They were living without evidence of disease two and six years following completion of treatment.

*Note: All dosages refer to estimated tumor dosages in roentgens.

Three patients had recurrent ovarian carcinoma as evidenced by ascites and/or the presence of an intra-abdominal mass. They received an estimated tumor dose of 2,600 to 4,600 r, but there was no change in 2 of the cases. Satisfactory palliation was attained for a three-month period in the other before her condition became worse and she died.

Ten patients with extensive disease, in whom excisional surgery was not deemed possible, were given 2 Mev therapy. In 2 of these patients, the treatment was incomplete; the other 8 received an estimated tumor dose of 4,000 to 5,400 r. In one half of these patients, no appreciable change occurred and in the other half satisfactory palliation was obtained for from six months to two years.

TABLE I. TREATMENT RESULTS IN OVARIAN MALIGNANCY

TYPE OF DISEASE	NO. OF PATIENTS	TUMOR DOSE	RESULT
Localized	2	5,000 r	No disease (2-6 years)
Recurrent	3	2,600-4,600 r	No change (2) Palliation 3 months (1)
Extensive	10	Incomplete-5,700 r	No change (5) Palliation 6 months-2 years (5)

Endometrium

The planned method of treatment at this institution for endometrial malignancy is to give the patient the benefit of intrauterine radium by means of the multiple capsule technique and then to follow this procedure in six to eight weeks' time with a complete abdominal hysterectomy and bilateral salpingo-oophorectomy. In certain instances, it may be preferable, because of the extent of the disease, or the constitutional condition of the patient, to utilize irradiation only.

TABLE II. TREATMENT RESULTS IN ENDOMETRIAL MALIGNANCY

TYPE	NO. OF PATIENTS	TUMOR DOSE	RESULT
Carcinosarcoma	1	5,600 r	No change
Carcinoma	7	3,540-5,400 r	Lost (1) No disease (4) 4 months-5 years Palliation (2) 8-27 months
Recurrent.—			
Sarcoma	1	1,600 r	No change
Carcinoma	9	700-6,000 r	No change (2) Palliation (7) 3-24 months

Of the 18 patients with primary endometrial malignancy who were treated, 8 were primarily treated at the Oncologic Hospital. One patient had a mixed mesodermal tumor arising in the uterus; she had complete excisional surgery with prompt recurrence. This patient received an estimated tumor dose of 5,600 r without appreciable benefit.

Seven patients received supervoltage therapy in a tumor dose varying from 3,540 to 5,400 r. One of these patients had no evidence of disease when last seen, but has been lost to follow-up eighteen months after completion of the treatment.

Four patients presented no clinical evidence of disease four months to five years after their therapy. Two patients obtained satisfactory palliation for from eight to twenty-seven months.

Ten patients had recurrent, extensive endometrial malignancy. One of these had a primary sarcoma of the uterus; treatment was carried to an estimated tumor dose of 1,600 r and then was discontinued because of the patient's general condition. Nine other patients were treated with amounts

varying from 700 to 6,000 r tumor dose. Two of the patients received less than 3,000 r depth dose and no clinical improvement was noted. The other 7 patients had relief of symptoms for from three to twenty-four months.

Cervix

The usual plan of treatment for patients in whom the histologic diagnosis of invasive carcinoma of the cervix has been made is to treat the patient first by means of external irradiation and then to follow this therapy by local radium application(s) by suitable applicators. In certain selected patients, with early disease, during the past few years, a radical type of hysterectomy with removal of the lymphatic drainage has been employed.

There were 27 patients treated originally at the Oncologic Hospital in whom 2 Mev therapy was employed.

The 6 patients with Stage I disease, who received an estimated tumor dose of 5,140 to 7,000 r, are all living without clinical evidence of disease nine months to six years after completion of therapy. It should be emphasized that these patients all had local radium therapy in addition to the supervoltage irradiation.

There were 9 Stage II patients, 6 of whom received 4,200 to 6,800 r estimated tumor dose and are living without any clinical evidence of disease three months to seven years after completion of treatment. Three patients (estimated tumor dose 3,900 to 6,080 r) died less than a year after completion of treatment.

TABLE III. TREATMENT RESULTS IN PATIENTS WITH CARCINOMA OF THE CERVIX UTERI WHO RECEIVED THEIR ORIGINAL CARE AT THE AMERICAN ONCOLOGIC HOSPITAL

STAGE	NUMBER	TUMOR DOSE	CLINICAL RESULT
I	6	5,140-7,000 r	No disease (9 months-6 years)
II	3	3,900-6,080 r	Dead (7-12 months)
	6	4,200-5,800 r	No disease (3 months-7 years)
III	3	4,472-5,300 r	Dead (9-30 months)
	2	5,040-6,040 r	No disease (2-6 years)
IV	7	1,800-5,400 r	Dead (3-18 months)

Two of the 5 Stage III patients (5,000 to 6,040 r tumor dose) are living two and six years, respectively, without evidence of disease. Three patients (4,500 to 5,300 r tumor dose) died in less than thirty months. The 7 Stage IV patients, whose tumor dose range was 1,800 to 5,400 r, lived three to eighteen months; all died with extension and/or metastasis from their cervical cancers.

Recurrent Cervical Carcinoma

By far the greatest percentage of patients who have been treated with 2 Mev therapy have been individuals with primary carcinoma of the cervix, recurrent or residual after treatment elsewhere. The majority of these patients have been well treated as judged by present standards of radiation therapy and were referred for consideration of 2 million volt therapy in the hope that "something might be done." In most instances, these patients had extensive disease and invariably the skin areas through which previous therapy had been administered were deeply bronzed and often telangiectatic. Sixty-two patients, whose primary treatment had been completed some time previously, were referred for therapy. Of this number, 9 are still living as seen in Table IV; one (estimated tumor dose 4,480 r) is living without clinical evidence of disease six years after completion of treatment. Two patients (5,000 to 6,426 r) are living three and two years, respectively, without evidence of disease. One patient whose treatment (4,400 r) was completed six months ago

demonstrates no clinical evidence of malignancy. Five patients (estimated tumor dose 5,000 to 6,500 r) achieved satisfactory palliation for two to four months after completion of their course of radiation.

TABLE IV. TREATMENT RESULTS IN PATIENTS WITH CARCINOMA OF THE CERVIX UTERI, RECURRENT OR RESIDUAL AFTER TREATMENT ELSEWHERE, LIVING AT PRESENT

Living at Present	9	
TUMOR DOSE	CLINICAL RESULT	NO. OF PATIENTS
4,480 r	No disease (6 years)	1
6,426 r	No disease (3 years)	1
5,000 r	No disease (2 years)	1
4,400 r	No disease (6 months)	1
5,500-6,500 r	Palliation (2-4 months)	5

TABLE V. TREATMENT RESULTS IN PATIENTS WITH CARCINOMA OF THE CERVIX UTERI, RECURRENT OR RESIDUAL AFTER TREATMENT ELSEWHERE, WHO ARE NOW DEAD

DEAD	TUMOR DOSE	CLINICAL RESULT
6	Incomplete	No change
11	3,000-6,200 r	No change
2	3,300-4,400 r	Lost
14	3,000-6,900 r	Palliation (1-3 months)
20	3,000-5,500 r	Palliation (4-48 months)

Fifty-three patients who were treated are now dead (Table V). Two patients were lost to follow-up and are presumed to be dead since their disease was unarrested when they were last examined. Seventeen patients received an estimated tumor dose of from 3,000 to 6,200 roentgens with no clinical improvement. Fourteen patients (3,000 to 6,900 r) were improved so that they were comfortable and free of symptoms for from one to three months. Twenty patients (dosage range 3,000 to 5,500 r) obtained satisfactory relief of their symptoms for periods of four to forty-eight months. Over one half this group had a satisfactory result for more than eighteen months.

Complications

Radiation therapy is a dangerous tool, particularly when we are dealing with voltages in the 2 million volt range, and complications do occur.

Thirty of the patients in this series were classified as being obese. Each of these patients weighed more than 160 pounds and had an anteroposterior pelvic diameter of more than 22 cm. Twelve of them weighed more than 200 pounds, the heaviest patient weighing 309 pounds. One patient required a lipectomy because of a large panniculus before therapy was instituted. Forty-six of the patients required blood transfusions either because of vaginal bleeding concomitant with the disease or because of anemia and leukopenia in association with the x-ray treatments. The white blood count fell below 3,500 in 13 patients.

The patient with recurrent vulvar malignancy developed a rather severe urethritis, vaginitis, and ulcerative vulvitis in conjunction with her treatment.

Both patients with primary vaginal carcinoma developed disturbing radiation sequelae. One had recurrent cystitis and painful vaginitis; the other, with recurrent disease, had a rather severe proctitis and therapy had to be interrupted twice because of nausea and vomiting. Each of these patients received an estimated tumor dose of 6,100 to 6,325 r.

Three of the 18 patients with malignancy of the endometrium had significant radiation difficulties. Two had severe proctosigmoiditis requiring hospitalization for treatment and one patient had severe proctosigmoiditis and a persistent sacral ulcer. The estimated tumor dosages in these patients ranged from 4,200 to 5,300 r.

There was an even greater percentage of radiation difficulties in the patients who had primary ovarian neoplasms (Table VI). Nearly one half of them had complications attributable to radiation; 6 had severe proctosigmoiditis, one of them also had associated vaginitis and cystitis; one patient who had been treated repeatedly for extensive ovarian malignancy died with multiple sites of intestinal obstruction. At autopsy examination, the multiple obstructive areas were found to be due to radiation fibrosis without residual carcinoma.

TABLE VI. RADIATION COMPLICATIONS OCCURRING IN PATIENTS TREATED FOR OVARIAN MALIGNANCY

	TUMOR DOSE
5 proctitis	3,600-5,600 r
1 proctitis, vaginitis, cystitis	5,700 r
1 intestinal obstruction	5,400 r (2 courses)

As noted in Table VII, there was a 66.6 percentage of complications in the patients who received their primary treatment for carcinoma of the cervix at the Oncologic Hospital. These patients all had local radium applications in order to achieve a theoretically satisfactory parametrial dosage. Thirteen patients had relatively severe proctosigmoiditis, requiring hospitalization and blood transfusions in some instances; 2 had large painful hemorrhoids which were most difficult to manage; 5 had hemorrhagic cystitis, one of whom ultimately had to have a bilateral ureterostomy for relief of her symptoms. This patient had received an estimated tumor dose of 6,300 r. One patient with proctitis developed bullous erythema multiforme two months after her 2 Mev therapy and is currently hospitalized, 14 months later, because of hemorrhagic proctitis. The bullous erythema multiforme was successfully treated with steroid drugs. One patient developed a moderate-sized sacral ulceration and two years after completion of treatment was found to have bilateral fractures of the femurs; one of these fractures was impacted and required no orthopedic treatment. It was necessary to pin the other femur for a satisfactory result. This patient has been living without evidence of disease for more than six years. One very obese patient, six months after completion of therapy, developed a large sacral ulcer with associated sacral osteitis. Three patients during the course of treatment had rather severe leukopenia and were transfused accordingly.

Most of these severe complications came early in the course of experience with the Van de Graaff machine. Many of these patients were excessively obese and represented treatment problems by *any* method.

TABLE VII. RADIATION COMPLICATIONS OCCURRING IN PATIENTS WHO RECEIVED THEIR ORIGINAL TREATMENT FOR CARCINOMA OF THE CERVIX UTERI AT THE AMERICAN ONCOLOGIC HOSPITAL

COMPLICATION	NO. OF CASES	TUMOR DOSE
Proctitis	5	3,000-5,800 r
Proctitis and cystitis	4	4,200-5,400 r
Proctitis and severe hemorrhoids	2	5,040-5,400 r
Anemia and leukopenia	3	5,000-5,200 r
Cystitis (ureterostomy)	1	6,300 r
Severe proctitis and bullous erythema multiforme	1	5,626 r
Sacral ulcer	1	4,815 r
Proctitis, sacral ulcer, bilateral fracture of femur	1	6,400 r

Twenty-one patients with carcinoma of the cervix, originally treated elsewhere, developed complications (Table VIII). Fifteen of them had rather

severe proctosigmoiditis; of this group 8 had associated cystitis; 2 had bothersome vulvitis and 3 had painful hemorrhoids. Three patients required transfusions because of anemia and leukopenia not associated with hemorrhage and 2 developed vulvar edema which subsided some months later. There was one sacral ulceration which healed without untoward difficulty a few months after completion of therapy.

TABLE VIII. RADIATION COMPLICATIONS OCCURRING IN PATIENTS WITH CARCINOMA OF THE CERVIX UTERI, ORIGINALLY TREATED ELSEWHERE

COMPLICATION	NO. OF CASES	TUMOR DOSE
Proctitis	7	1-800-5,700 r
Proctitis and cystitis	3	3,700-6,100 r
Proctitis, cystitis, and hemorrhoids	3	4,900-5,300 r
Proctitis, cystitis, vulvitis	2	4,900-5,500 r
Sacral ulcer	1	4,700 r
Vulvar edema	2	3,800-5,200 r
Anemia and leukopenia	3	5,000-5,300 r

Comment

There has been increasing use of high-voltage irradiation in the management of malignancy of all varieties. The first million volt generators were more or less stationary, but recently they have become more flexible so that rotational therapy has been developed and is being used successfully. Orton[2] at Sheffield has described the installation of a rotation therapy apparatus. Trump and associates[3] have described their technique with rotational supervoltage therapy in the management of tumors of the pelvic cavity. Guttman,[4, 5, 6] in a number of presentations, has described her experience with 2 million volt radiation therapy. Nolan and others[7] have recently reported a slight superiority in comparing cobalt^{60} teletherapy with 450 kv. x-ray therapy in cervical cancer, which seemed to be related to a more uniform distribution of irradiation.

At the Sheffield National Center for Radiotherapy, according to Blomfield,[8] hopeful results have been obtained in gynecologic cancer. His patients were significantly free of such grave complications as rectovaginal and vesicovaginal fistulas.

In evaluating supervoltage therapy for carcinoma of the cervix, Guttman[6] considered the immediate tolerance of the patient to supervoltage therapy better than in conventional 200 to 250 kv. therapy. It was her impression that survival rates could best be improved by means of this type of treatment. Ninety-two patients with carcinoma of the cervix were treated, about half of whom had had their primary treatment elsewhere. In only 7 of these patients did late complications occur.

At the Oncologic Hospital the number of cases is not large and the length of time since completion of treatment has been brief so no comparison can be made between the results of therapy with conventional radiation and supervoltage irradiation.

The number of complications does seem excessive and unduly severe in character. However, the majority of the severe complications occurred early in the experience with this type of treatment. The sacral ulcerations all

occurred in obese patients and were undoubtedly associated with tangential irradiation in the gluteal fold and sacral area. In recent years, there have been no such complications.

It is expected, with high-voltage irradiation and its increased depth dose, that a definite percentage of patients will develop cystitis and proctitis. The tolerance of the rectal mucosa is considerably less than that of the vaginal mucosa. By more exact positioning of the patient it is hoped that this complication may be minimized.

Since a better depth dose may be achieved, using fewer fields and preserving the skin to a greater degree, the obese patient is the logical candidate for supervoltage irradiation therapy.

Smith,[9] in a recent article, discussed 8 fractures of the neck of the femur following heavy irradiation therapy for cervical carcinoma. It is implied that radiation fractures of the femur are more likely to occur when there is associated osteoporosis. Bonfiglio[10] estimated the average dose to the neck of the femur during pelvic irradiation for cervical carcinoma to be 3,000 r and the tolerance dose has been estimated at 3,840 to 4,320 r.

The patient at the Oncologic Hospital who sustained bilateral fractures of the femur was 57 years of age at the time her treatment was administered. She is living and free of demonstrable disease at the present time.

The one patient who died with intestinal obstruction associated with roentgen fibrosis, in this series, had received a high dosage of irradiation over most of the abdomen, through eight large portals of entry. The estimated tumor dose in this individual was 5,400 r. In retrospect, this patient was undoubtedly overirradiated; however, the apparent clinical extent of her disease seemed to require this amount of irradiation at the time.

The results of treatment in vulvar and vaginal cases were rather disappointing. Because of the relatively superficial nature of these primary lesions, supervoltage therapy has little or no advantage over conventional methods of treatment.

In the planned treatment of ovarian carcinoma, supervoltage therapy is helpful because of the ease with which a satisfactory depth dose may be obtained. In the 13 patients with extensive disease who were treated at the Oncologic Hospital, satisfactory palliation was achieved in 6 instances.

It should be stressed again that palliation means relief of symptoms and does not refer to length of survival.

In patients with primary endometrial carcinoma in whom excisional surgery combined with intracavitary radium does not seem feasible, 2 Mev irradiation provides a method by which satisfactory radiation may be achieved. In the 7 patients primarily treated by the Van de Graaff machine, 4 were considered free of disease four months to five years following therapy and palliation for varying lengths of time was obtained in 7 of the 9 patients afflicted with recurrent endometrial carcinoma.

In conjunction with radium locally, in cancer of the cervix, supervoltage is a satisfactory method of achieving an adequate parametrial dose. Fourteen of 20 patients with Stage I, II, and III lesions were clinically free of disease nine months to seven years after therapy had been administered.

Although Schmitz and Murphy[11] reported a 16 per cent five-year survival after re-treatment of cervical carcinoma, this high survival rate was not reached with our patients, since only 4 of 62 patients in our group were clinically free of disease after completion of therapy, and 3 of these patients have been observed for less than three years.

When the tumor is radiation resistant, whether the treatment be by 200 kv. 250 kv., 2 Mev, or cobalt^{60}, the resistance of the tumor will be the same, provided that the same amount of irradiation is delivered to the same volume of tissue in the same length of time.

Two million volt irradiation gives a greater depth dose in comparison with the conventional type of treatment. Table IX, which was developed by James L. Weatherwax, Physicist at the American Oncologic Hospital, shows the percentage of irradiation delivered at different tissue levels by different methods of treatment.[12, 13, 14]

TABLE IX. COMPARATIVE DEPTH DOSES OF IRRADIATION WITH DIFFERENT TYPES OF THERAPY

TYPE OF THERAPY DISTANCE FROM SKIN SKIN AREA	200 KV. 50 CM. 100 CM.^{2}	250 KV. 50 CM. 100 CM.^{2}	2 MEV 70 CM. 100 CM.^{2}	COBALT^{60} 70 CM. 100 CM.^{2}
Backscatter	36%	30%	4%	3%
Skin surface	100%	100%	100%	100%
5 cm. depth	61%	62%	73%	76%
10 cm. depth	30%	33%	50%	55%
15 cm. depth	15%	17%	34%	37%
20 cm. depth	7%	8%	23%	26%

With increasing voltages the skin shows increased tolerance to irradiation. In 200 to 250 kv. therapy the amount of treatment that a patient's abdomen can withstand is limited by the amount that the skin can tolerate. In 2 Mev therapy the amount of radiation that a patient can withstand through abdominal portals is limited by the reaction of the bladder and bowel. In the follow-up examination of patients who have had the benefit of 2 Mev therapy, there is a rather distinctive brawny bronzing that develops in the skin and subcutaneous tissues. Clinically it is quite difficult to differentiate between this brawny fixation and the induration which is usually associated with neoplastic infiltration.

As the voltage increases, the exit dose may become as great, or greater than the entrance dose. It is this factor that obviates against using voltages higher than 3 to 5 million volts. If opposing portals are used, exit and entrance dosages may coincide, eliminating any benefit that the increased skin tolerance may have. With proper positioning of patients, necrosis of bone should be avoided.

The use of 2 Mev therapy should be cautious since a superlethal effect may result, and the danger of destruction of normal tissue may be greater than the benefit resulting from the destruction of diseased tissue.

Ralston Paterson[15] in a recent presentation demonstrated that the peak survival rate resulted in patients with carcinoma of the cervix uteri when the tumor dose at Point A was 8,000 r. At this dosage a 56 per cent survival rate was achieved. When the dosage was only 6,000 r, 45 per cent survival resulted, and when the dose rose to 9,000 r the survival rate fell to 46 per cent.

Surgery and irradiation are methods which may be effectively used in the control of gynecologic malignancy. It is hoped that by techniques such as the screening methods developed by the Grahams[16] and Gusberg[17] the differentiation between radiation-resistant and radiation-sensitive tumors may become more accurate.

In the light of our experience with patients who have recurrent disease, it appears that a tumor which is radiation resistant to 200 kv. therapy will be equally radiation resistant to 2 Mev therapy, provided that the same depth dose of radiation is given.

Does the shorter wave length irradiation produced by 2 Mev give a better therapeutic result because of the quality of the radiation than comparable doses with lower voltages? This point is still unproved and we can thus far assume that there is no specificity of wave length.

There is little practical advantage in using voltages greater than 2 Mev since sources of higher energy such as the synchrotron, cyclotron, and betatron may give so high an exit dose that greater skin damage may result. This increased exit dose is particularly important when crossfire irradiation with higher voltages is contemplated.

In supervoltage therapy there is a greater relative depth dose with less skin reaction because of less backscatter and fewer fields are needed to deliver a predetermined dose.

The advantages of supervoltage therapy over conventional therapy are entirely physical. The depth dose is greater because of greater penetration. Skin damage is reduced and there is less bone absorption and less chance of bone necrosis. Since there is less backscatter, the volume of normal tissue irradiated is smaller.

Summary

1. The case histories of 126 patients with primary gynecologic malignancy, treated principally with 2 Mev therapy have been reviewed.

2. Fifteen patients with primary ovarian malignancy were treated, with improvement in 7.

3. Eighteen patients with primary endometrial malignancy were treated, with worth-while results in 13.

4. Twenty-seven patients with primary cervical carcinoma were originally treated at the Oncologic Hospital. Twelve of the 15 patients with early disease are clinically well at present.

5. Sixty-two patients with recurrent cervical carcinoma were treated. Fifty-three of these patients are now dead, 34 received satisfactory palliation for three to forty-eight months. Four of the 9 living patients are clinically free of disease and 5 have achieved satisfactory palliation for short periods of time.

6. Three of the 18 patients with corpus carcinoma and 7 of the 15 patients with primary ovarian malignancy had radiation complications. One death in this group was associated with postradiation intestinal fibrosis.

7. Eighteen of the 27 patients with primary cervical cancer and 21 of the 62 patients with recurrent cervical cancer developed postradiation sequelae.

8. The advantage of 2 Mev therapy in the management of the obese patient is stressed.

9. The shorter wave length of the 2 Mev irradiation apparently produces no better therapeutic effect than comparable doses with lower voltages.

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Discussion

DR. HOWARD C. TAYLOR, JR., New York, N. Y.—Dr. Hahn has brought an important subject to the attention of the Society, for there is no doubt that supervoltage radiation is going to play a continuously more important part in the therapy of gynecological cancer. On the other hand, I think that he himself has indicated that he has raised the point and not given the answer to the question of the extent of the superiority of supervoltage to conventional radiation therapy.

Gynecologists have for nearly half a century been trying to determine whether radical surgery or radiation is a better basic method for treating cancer of the cervix. In this effort the relatively precise means of comparing five-year cure rates has been available and yet no clear answer has been found. In attempting to compare the effects of 200 kv. with those of 2,000 kv. x-ray, one is confused by the fact that the x-ray is either simply an adjunct to a radium or surgical program or else is used as a so-called "palliative" procedure. It will certainly be a long time before convincing statistical evidence is available, and we must depend in the meantime upon inferences derived from physical measurements and upon clinical impressions.

At the Columbia Presbyterian Medical Center, there are two separate institutions treating gynecological cancer, the Sloane and the Francis Delafield Hospitals. The gynecological attending and resident staffs of the two institutions are identical, the radiotherapy staffs more or less separate. The x-ray equipment available to the Sloane Hospital patients was a conventional 250 kv. machine, until ten months ago, when therapy by means of the betatron giving an x-ray beam equivalent to about 18,000 kv. was begun; at the Francis Delafield there has been a 2,000 kv. x-ray machine since 1951 and since 1953 cobalt^{60} designed to give rotational therapy. The many possibilities offered by this varied equipment could well lead to increased confusion, but this is partly avoided by a joint committee representing the gynecological and radiological staffs of the two hospitals which has drawn up a general program for the treatment of gynecological cancer, providing for some consistency and at the same time an opportunity for comparing different techniques.

In the Francis Delafield Hospital, where 92 patients with cancer of the cervix have been treated in the last four years by supervoltage therapy, the present plan is as follows: In Stages I and II, the 2,000 kv. machine is used to give a dose of 5,000 r in five weeks, the treatment being begun 8 days after completion of the radium therapy. In cases in which radical hysterectomy has been carried out instead of radium, postoperative x-ray therapy with the same machine and the same dosage as after radium therapy is given. In cases of Stage III and in those cases of Stage IV in which exenteration is not done, the treatment at the Delafield Hospital is by the cobalt^{60} rotational machine, with a dose of 6,000 r throughout the pelvis, preceding an eventual radium application. At the Sloane Hospital, where 23 cases of cancer of the cervix have been treated by the betatron, this apparatus has become standard for all cases of cancer of the cervix requiring external therapy.

From this experience, certain tentative points may be made, for the most part in agreement with Dr. Hahn's own conclusions:

1. There appears to be no specificity of wave length in relation to tumor response. As Dr. Hahn has said, if a tumor is resistant to one voltage therapy, it will be resistant to another, always provided that the same dose is given.

2. The higher voltages, however, make it much easier to give a uniform dose to desired anatomical areas. With multiple fields, the same may usually be accomplished by the lower voltages, except in the instance of the very obese patient where the higher voltages alone may be successful in giving the required amount of radiation to the center of the pelvis.

3. The skin is relatively less affected by the higher voltages, which make this type of therapy especially desirable for the patient with recurrent or persistent disease after previous courses of therapy. However, as Dr. Hahn has also pointed out, with supervoltage the amount of abdominal radiation the patient can stand is limited by the tolerance of bowel and bladder.

4. It had been our hope that the precise localization on the cervix which can be accomplished by rotational cobalt^{60} might obviate the necessity of radium entirely. However, we have found even after 6,000 r that histologically viable cancer is usually still present in the cervix. An occasional disadvantage to preliminary external supervoltage therapy furthermore is that the vaginal vault becomes so contracted as to make radium application difficult.

5. Finally, it is our impression that radiation sickness is certainly less intense and severe complications less frequent than with conventional therapy. The proctitis and cystitis noted by Dr. Hahn appear to be a measure of the higher dose successfully delivered to the center of the pelvis and are to be evaluated in the same way as the unavoidable erythema of the skin.

DR. HERBERT E. SCHMITZ, Chicago, Ill.—As we all know, in order to attain successful results in the treatment of malignant disease with ionizing radiation, we must try to irradiate the entire tumor or tumor-bearing area as homogeneously as we can. Then we must deliver the optimal dose that is considered cancerocidal. Generally, we accept a 6,000 r tumor dose delivered in 32 days as lethal for carcinoma of small or moderate size. Our observations have indicated that external irradiation by x-rays with energies up to 1 Mev is inadequate to destroy most tumors in the pelvis. Radium is therefore added to increase the tumor dose. This combination of radium and high voltage x-ray has been employed in our clinic since 1933.

In roentgen therapy, an x-ray machine is used. The output of the machine, i.e., so many roentgens per minute at a fixed focal skin distance, is the air dose. The skin dose is always higher than the air dose because of the backscatter. How much higher depends on the voltage of the machine or the quality of the x-ray beams. Usually the harder the x-ray beams, the smaller the backscatter. The depth dose is usually referred to as a certain percentage of the air dose or skin dose. It is this dose which tumor or tumor-bearing area and surrounding tissue would receive.

When a combination of radium and x-ray is used, great care is necessary to insure protection to the noninvolved structures of the pelvis from overdosage. The mucosa of

the bladder and bowel can stand from 5,000 to 6,000 r without permanent injury other than slight fibrosis and telangiectasia. Above this dosage stricture and stenosis result with, at times, obstruction and fistula formation. It is desirable, therefore, in the treatment of uterine and vaginal cancer, to rely on the radium dose, carefully protecting the midpelvic plane with adequate thickness of lead, using x-ray to supplement the inadequate dose received at point B, 1,300 gamma roentgens by our technique, but to add very little to the dose at point A which, with our plan of radium therapy, receives 7,000 gamma roentgens.

It is quite evident that our problem is not one of increasing dosage but rather one of controlling dosage throughout the pelvis. With less scatter the higher energy beam may be directed to a tumor-bearing area in need of additional irradiation while with packs, tilting, and filter we protect areas that have already received a tolerance dose. Our studies and those of Garcia demonstrate that overirradiation of the tumor-bearing areas decreases the survival percentage and that the optimal dose seems to be 4,500 r. We may obtain such a dose in the average pelvis with 200 kv., 250 kv., 1 Mev, or 2 Mev energies. The only advantage of 1 or 2 Mev is that we have decreased the treatment time, lessened the undesirable side effects of nausea and radiation sickness, and reduced the skin reaction by eliminating the soft rays.

Since 1933 we have treated 340 patients with primary carcinoma of the cervix, as shown in Table I.

TABLE I

CLINICAL GROUP	I	II	III	IV	TOTAL
Number admitted	37	82	141	80	340
Five-year survival	32	53	58	8	151
Per cent survival	86.5	64.6	41.1	10.0	44.4

If we accept Groups I and II Schmitz Classification as Stage I International, we then have 119 cases with 85 surviving, a percentage of 71+ per cent. For the year 1950 we achieved 100 per cent 5 year survival in Groups I and II and 53+ per cent in Group III, an over-all survival of 60 per cent. Carcinoma in situ is not included in this study, such cases are collected under Group O.

These results have been achieved by close cooperation of clinician, pathologist, cytologist, and radiologist. Early accurate diagnosis, proper planning of therapy, exact application, and meticulous follow-up are the essential reasons for this accomplishment.

As the author states, there is a greater risk in employing ionizing radiation of 2 Mev because the outward signs of effect are minimized and deep injury may occur because of the desire to increase the tumor dose. *Overdosage is as disastrous as underdosage.*

Endometrial carcinoma is adequately treated by the multiple radium capsule packing of the fundus or by employing radium applicator as used in our clinic. The dosage administered within the uterine cavity enclosed by thick muscle walls causes complete destruction of tumor for a depth of about 6 mm. External irradiation must be directed to the parametrial areas or injury to bowel and bladder results.

Vulvar cancer in our experience is a surgical disease to which x-ray can add little. In such superficial disease, lower voltage x-rays well filtered at a suitable skin target distance will deliver dosage within safe ranges. Interstitial radium is preferable for local recurrence.

In the vagina interstitial radium is preferable to external irradiation and can be supplemented with contact radium placed in a mold or phantom. Dissection of regional nodes with or without total vaginectomy and total hysterectomy is preferable to external irradiation.

In ovarian malignancy, total extirpation of the uterus and adnexa followed by nitrogen mustard intravenously to arrest cells loosened into the circulation, gold—Au^{198}—into the peritoneal cavity to destroy superficial implants and cells present in the peritoneal cavity, and a complete cycle of external irradiation constitute the method we employ at present. In these patients, higher voltage irradiation improves the intensity of irradiation throughout the pelvis because of the increased depth dose and lessened general effect on the host.

In regard to the treatment of recurrent or persistent disease of the cervix, Table II depicts our experience during the years 1946 to 1950, inclusive.

TABLE II

CLINICAL GROUP	I	II	III	IV	TOTAL
Number admitted	5	15	22	46	88
Five-year survival	2	10	9	3	24
Per cent survival	40.0	66.6	40.9	6.5	27.2

In these instances we believe higher voltage irradiation is an advantage because less skin and tissue damage results from the reirradiation. We also employ radium when the tissues will tolerate it and most frequently this is by means of low-source, long-time interstitial needles.

By conforming to dosage tables already well established I believe the author will continue to obtain his satisfactory results with less injury to normal tissues.

DR. A. N. ARNESON, St. Louis, Mo.—I cannot let pass without comment the observation in reference to the lack of specificity for quality of radiation in the treatment of cancer. We are also accumulating experience with the betatron operating as an x-ray machine at a potential of 20 million volts. We are arriving at the conclusion already given, that there is no specificity for quality. I am interested, however, in the comment of some of our confreres from general surgery. In the treatment of gastrointestinal cancer they believe the effects of supervoltage superior to those following more conventional irradiation. If that is correct the same principle may apply to glandular cancers of endometrium and ovary.

In considering Dr. Hahn's paper it seems to be in order to return our attention to the paper by Dr. Smith on the evaluation of the basal cell in radiosensitivity studies. His slides showed rise and fall of different cell types with curves crossing at times, and usually about 3 weeks after the beginning of treatment. I believe that period corresponds to their full treatment program. Dr. Taylor stated that his group had attempted to treat cancer of the cervix with the external application of high voltage x-rays alone. Serial biopsies revealed residual cancer, however, and he was obliged to apply radium. The time factor may be of significance. The effects of radium are accomplished more rapidly due to the higher intensity of irradiation. In the case of glandular cancers treated with the betatron there is more rapid accumulation of depth dose than for 200 kv. x-rays. Our error may be overprotraction of treatment. Apparent variations in response may be the result of rate of administration rather than quality of radiation.

DR. HAHN (Closing).—Dosage in irradiation may be placed in four major categories: the quantity of irradiation (or total dose in roentgens received); the volume of tissue irradiated; the quality (voltage) of irradiation; and the time. Time refers to the intensity of irradiation (roentgens per minute), the over-all time for the course of treatment, and the degree of fractionation (the interval between treatments).

Nolan, Andrews, Moody, Du Sault, and others have been investigating time-dose relationships. Prolongation of treatment time may be disadvantageous, particularly in tumors which histologically are adenocarcinoma.

Ralston Paterson of the Holt Radium Institute in Manchester, England, at the Seventh International Congress of Radiology in 1954, presented survival figures in patients treated for carcinoma of the cervix. A five-year survival rate of 56 per cent was obtained in 158 patients when the dose at Point A was 8,000 r. When the dose at Point A was 6,000 r, the survival rate in 47 patients was 45 per cent. When, however, the dose was 9,000 r (in 112 patients) the survival rate was only 46 per cent. In these patients the highest survival rate was achieved when the tissue dose at Point A was 8,000 r.

In conventional therapy, there is a 36 per cent backscatter and only a 3 to 4 per cent backscatter with the higher voltages. The anteroposterior pelvic diameter averages about 20 cm. At a midplane depth of 10 cm., with 200 kv., a 30 per cent dose would result, whereas it would be 50 per cent with 2 Mev therapy and 55 per cent with Co^{60} therapy. The greater relative dose obtainable in the obese patient by means of 2 Mev and Co^{60} irradiation is readily apparent.

VAGINAL LESIONS OF ADENOMATOUS ORIGIN*

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THE vaginal wall is a singularly monotonous structure from the point of view of the pathologist, almost invariably showing a fibromuscular wall lined with stratified squamous epithelium. Usually he is limited in his material to fragments removed during plastic procedures and almost never is given the opportunity to examine the entire organ with the meticulous care that has been devoted to the cervix. On the other hand, the clinician is absorbed with diffuse changes in the lining epithelium related to the presence of pathogenic bacteria or of parasites and with the variations in epithelial activity induced by the presence or absence of the ovarian hormones. The commonest tumor, an epithelioma, obviously arises from the normal lining epithelium. It is rare, constituting about 1 per cent of gynecological malignancy.

There is, however, a small group of vaginal lesions which are infrequently or rarely observed and which cannot be derived from tissues ordinarily observed in this organ. These are characterized by the presence of cystic or glandlike structures in the vaginal wall, usually situated beneath and not involving the normal vaginal mucosa. They are lined by epithelium showing varying characteristics. From these structures it can be presumed, and sometimes proved, that the rare adenocarcinomas of the vagina arise. For their presence it is necessary to seek an embryological explanation.

Some can be attributed to persistent remnants of the mesonephric or Gartner's duct which in the embryo passes through the broad ligament, enters the lateral wall of the cervix, and then courses through the lateral wall of the vagina, inclining posteriorly as it descends. Its terminal portion angles forward sharply to terminate in the hymen. The distal portion of this embryonic structure disappears in most adults but remnants may persist anywhere along its course. Those in the broad ligament, together with the tumors derived from them, have been recently described by Gardner, Greene, and Peckham[1] (Fig. 1). They are lined with low cuboidal epithelium, with scanty cytoplasm, the oval deep-staining nucleus being central, with the long axis frequently transverse. A thin mantle of smooth muscle surrounds these structures. A similar picture is noted in the vestiges sometimes found in the cervix as well as in certain vaginal cysts, except that the muscular mantle is obscured. Huffman[2] found mesonephric tubules in about 1 per cent of instances by reviewing a large number of adult cervical specimens. I believe that more meticulous examination of this part of the uterus will reveal an even greater incidence

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since several instances have been observed in the laboratory at Bellevue Hospital among less than 100 specimens carefully examined in a study of early carcinoma. It is not known how often remnants persist in the vaginal wall since careful microscopic study of its entire structure is rarely carried out and such lesions are detectable clinically only when they become distended with secretion to form cysts which are usually single and rarely large. It is to be suspected that hidden remnants occur at least in an order of frequency similar to that found in the cervix and that they far exceed the palpable cysts. The stimulus leading to secretory activity is unknown. The other source of adenomatous foci in the vaginal wall is the invasion of the embryonal vaginal tract by the epithelium of the urogenital sinus. This displacement of Müllerian epithelium proceeds to the vicinity of the external os, more slowly in the midline of the lower vagina posteriorly, and less efficiently in the deep narrow fornices. In these areas fragments of Müllerian epithelium may be isolated beneath the new lining of squamous epithelium. These may persist in the mature female giving rise to structures lined with tall columnar epithelium filled with mucoid secretion, to foci showing the characteristics of endometrium, or even to spaces lined with cells suggesting tubal characteristics. To Robert Meyer[3-8] must go great credit for his work in this embryological area and for the demonstration that both mesonephric and Müllerian vestiges may give rise to lesions in the adult vagina.

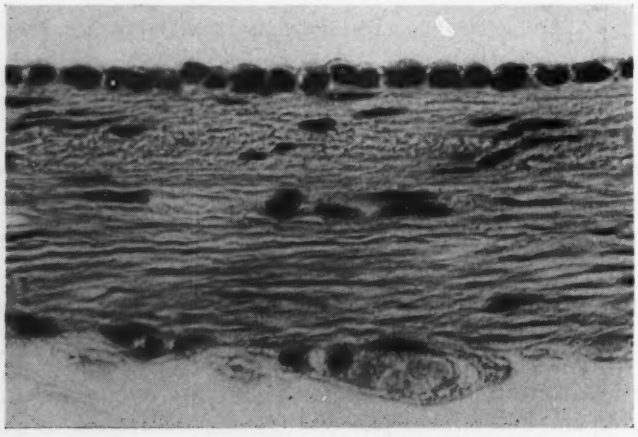


Fig. 1.—Mesonephric cyst of broad ligament showing characteristic lining epithelium and surrounding mantle of smooth muscle.

Clinically one may classify these lesions into several groups as illustrated in Table I.

TABLE I. CLASSIFICATION OF VAGINAL LESIONS OF ADENOMATOUS ORIGIN

A. Benign.—
1. Solitary cysts of vaginal wall
   (a) Mesonephric
   (b) Müllerian
2. Primary endometriosis of the vagina
   (a) Müllerian
3. Adenosis of the vagina; localized or diffuse
   (a) Müllerian

B. Malignant.—
1. Adenocarcinoma of the vagina
   (a) Mesonephric
   (b) Müllerian

The purpose of this presentation is to report a small group of these rare lesions together with a brief account of their treatment and follow-up. This material is derived from the gynecological service at Bellevue Hospital, from private practice, and from the practice of several physicians who have been so kind as to allow the inclusion of their material.

Fig. 2.

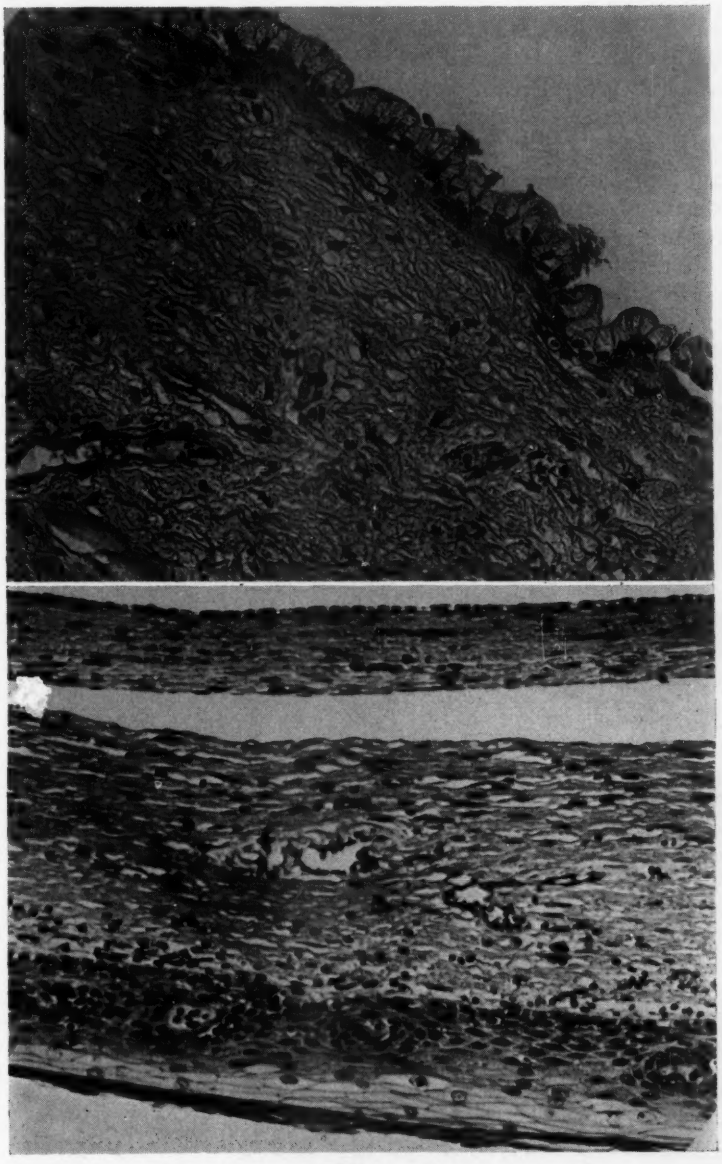


Fig. 3.

Fig. 2.—Solitary cyst of vagina lined with tall columnar epithelium suggesting Müllerian origin. (×200; reduced ¼.)
Fig. 3.—Solitary cyst of vagina lined with cuboidal cells suggesting a mesonephric origin. (×200; reduced ¼.)

Solitary Cysts of the Vagina

Little need be said about the most common type, the solitary cyst of the vagina. They occur in the lateral or posterior vaginal wall, rarely exceeding

4 cm. in diameter, and have been noted 12 times in 20,000 gynecological admissions to Bellevue Hospital over the past ten years. They are usually regarded as arising from vestiges of the mesonephric duct but many of them are lined with tall columnar mucus-secreting epithelium (Fig. 2) and are probably Müllerian in origin. Others are lined by the cuboidal epithelium characteristic of mesonephric structures (Fig. 3). Unless they are of large size we have not regarded surgical removal as an urgent matter. Observation of many of these patients over long periods of time has shov n such cysts to remain static, producing no symptoms. We have found none whose course leads us to believe that such conservatism was wrong.

Primary Endometriosis of the Vagina

Primary endometriosis of the vagina is much more rarely observed. No instances have been seen at Bellevue Hospital, the 2 examples to be shown both having been encountered in private practice.

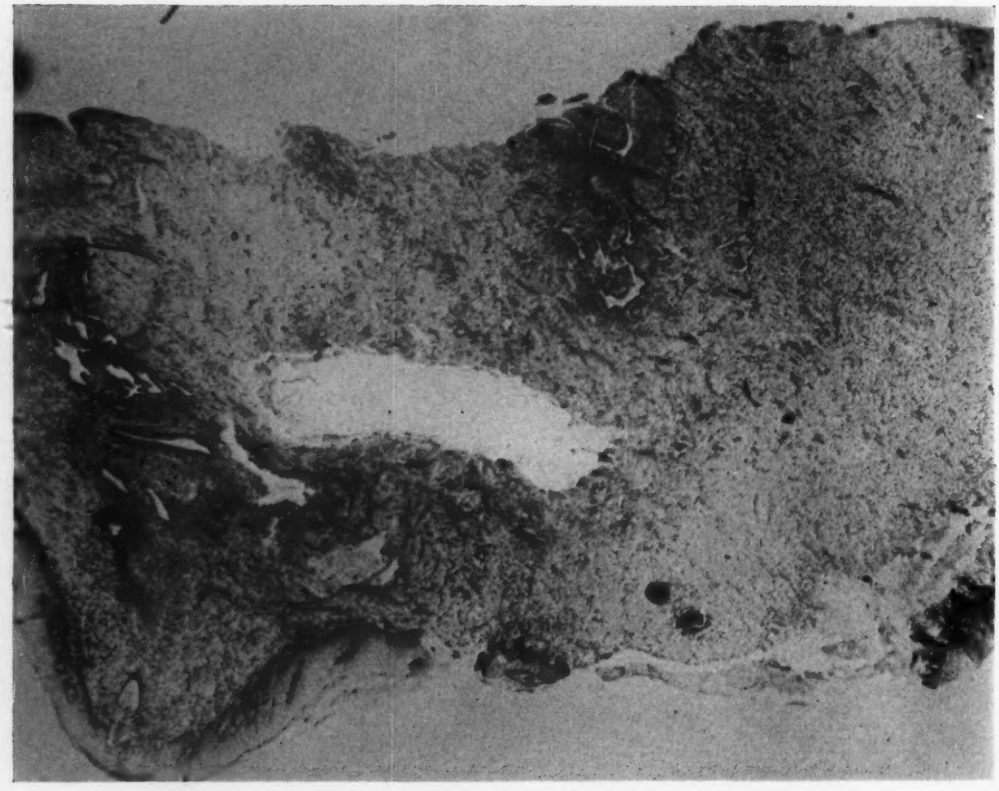


Fig. 4.—Primary endometriotic foci in vaginal wall of posterior fornix. (×15; reduced ⅙.)

CASE 1.—Mrs. C. C., aged 43 years, para 0, gravida 0, a cancerphobe, was seen in 1944. Her sole complaint was that she had felt something abnormal at the vault of the vagina. Examination showed an area of thickening containing small nodules in the posterior fornix. On speculum examination scattered deep blue areas could be seen beneath an intact mucous membrane. The remainder of her gynecological examination was negative; the sacrouterine ligaments were clear, the uterus anterior and freely movable, the adnexa negative. A biopsy from the vaginal vault showed typical endometrial foci (Fig. 4). A year later she suffered from acute appendicitis, and, during her operation, careful

exploration of the pelvic organs showed no evidence of endometriosis. Her menopause occurred in 1949 and when she was last seen in 1950 the lesion of the vaginal vault could no longer be detected.

CASE 2.—Mrs. E. W., aged 31 years, was first seen in 1937. Her menstrual history was normal. She had never been pregnant and had undergone no gynecological operations. Examination at this time disclosed no significant findings. In the next two years she aborted twice in the first trimester and in 1943 carried a twin pregnancy successfully to term. At the time of her delivery a median episiotomy was performed and a soft gray node of tissue was noted in the vaginal wall at the apex of the incision. This was excised and the episiotomy was repaired (Fig. 5). Microscopic examinaton showed a well-developed decidua with glands and stroma (Fig. 6). This patient was seen on many occasions up until May, 1950. Despite careful search no evidence of further vaginal lesions could be discovered. Her other pelvic findings were normal.

Comment.—Most cases of endometriosis of the posterior fornix of the vagina represent extensive involvement of the cul-de-sac with penetration of the septum, secondary to pelvic endometriosis. In fact, were it not for the subsequent negative exploration, the first case could not be included. However, it offers further demonstration that the lesion can be primary in this area. The possibility of such an origin must be considered in patients who are otherwise symptomless and in whom there is no evidence of an intrapelvic lesion. In the second case the endometrial nodule was in a most unusual location and can be safely assumed to be primary, particularly in view of the fact that no further evidence of the disease developed.

Adenosis of the Vagina

Adenosis of the vagina is an extremely rare condition. No instance has been observed on the gynecological service in Bellevue Hospital. The following example occurred in a private patient.

CASE 3.—Mrs. J. M., age 34 years, was first seen in 1937 for complaints unrelated to the condition to be reported. Gynecological examination disclosed normal findings. She was seen on frequent occasions over the next nineteen years. In January, 1939, on routine examination it was noted that the upper anterior vagina was thickened and contained tiny nodules. Inspection showed no surface changes. On her next visit in 1940 this lesion could not be detected. In October, 1944, she returned and it was found that the lower half of the posterior vaginal wall was studded with innumerable small shotlike nodules some of which presented beneath the mucosa like small shining vesicles. The anterior wall was involved to a lesser degree. The remainder of the examination showed normal findings. She was admitted to the hospital for dilatation, curettage, and vaginal biopsy (Fig. 7). The latter showed the vaginal wall to be filled with minute cystlike structures lined with low cuboidal epithelium (Fig. 8). In places this was flattened while in others the nuclei were pyknotic and the cytoplasm vacuolated and granular (Fig. 9). In a few places the epithelium had become multilayered and transitional in type. Both the cells and contents took a positive mucicarmine stain. A diagnosis of diffuse adenosis of the vagina was made. The cervical biopsy and curettings proved normal. Because the lesion appeared benign and complete resection would have been mutilating, nothing further was done. Her menses ceased in 1945 and at visits in that year and in 1946 the lesion appeared unchanged. In 1951 she was examined by another physician who felt the vagina was normal. However, on a recent visit in June, 1956, tiny shotlike structures could still be felt in the lower posterior vaginal wall. The lesion has regressed but has not disappeared.

Comment.—Plaut and Dreyfuss[9] have reported 3 cases of this condition and reviewed the literature. They credit Bonney and Glendenning[10] with reporting the first case in 1910. In most of the cases mentioned in their report the glands and cysts were lined with tall columnar mucus-secreting cells with basal nuclei suggesting those lining the cervical glands. They gave a positive stain with mucicarmine. In a few instances the process had

Fig. 6.

Fig. 5.

Fig. 5.—Decidual nodule in lower third of posterior vaginal wall showing relation to mucosa. (×100; reduced ⅓.)
Fig. 6.—Higher magnification of decidual nodule. (×150; reduced ⅓.)

broken through and replaced the vaginal mucosa. They believed this lesion to be derived from Müllerian rests, and to be benign and unlikely to develop malignant characteristics. The linings of the small cysts in this specimen certainly do not suggest cells of the cervical glands. However, the fact that the epithelium and cyst contents give a positive mucicarmine test shows them to be mucin producers and probably Müllerian in origin.

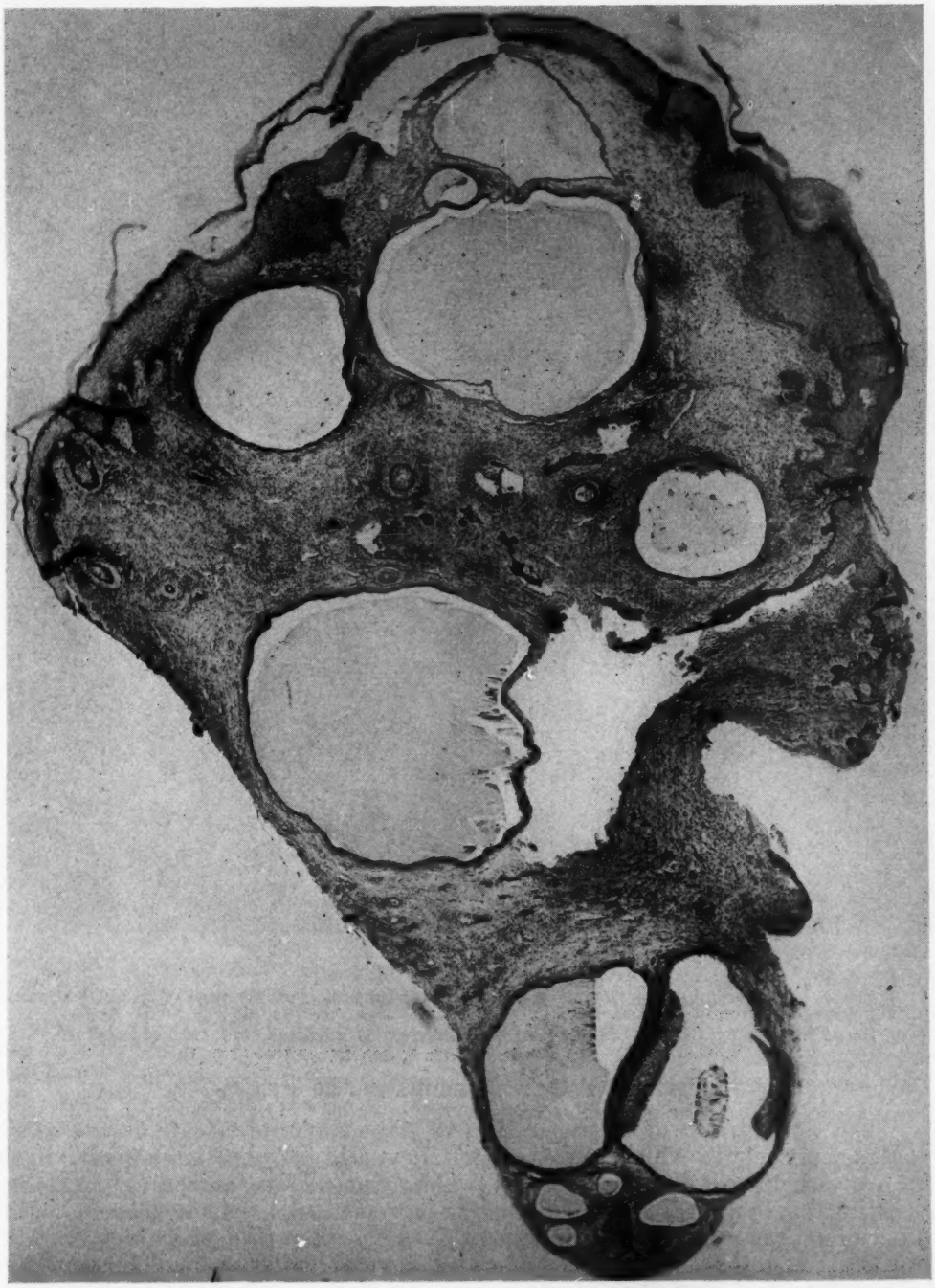


Fig. 7.—Diffuse adenosis of vagina showing relation to vaginal wall and mucosa. (×15; reduced ⅙.)

Fig. 8.

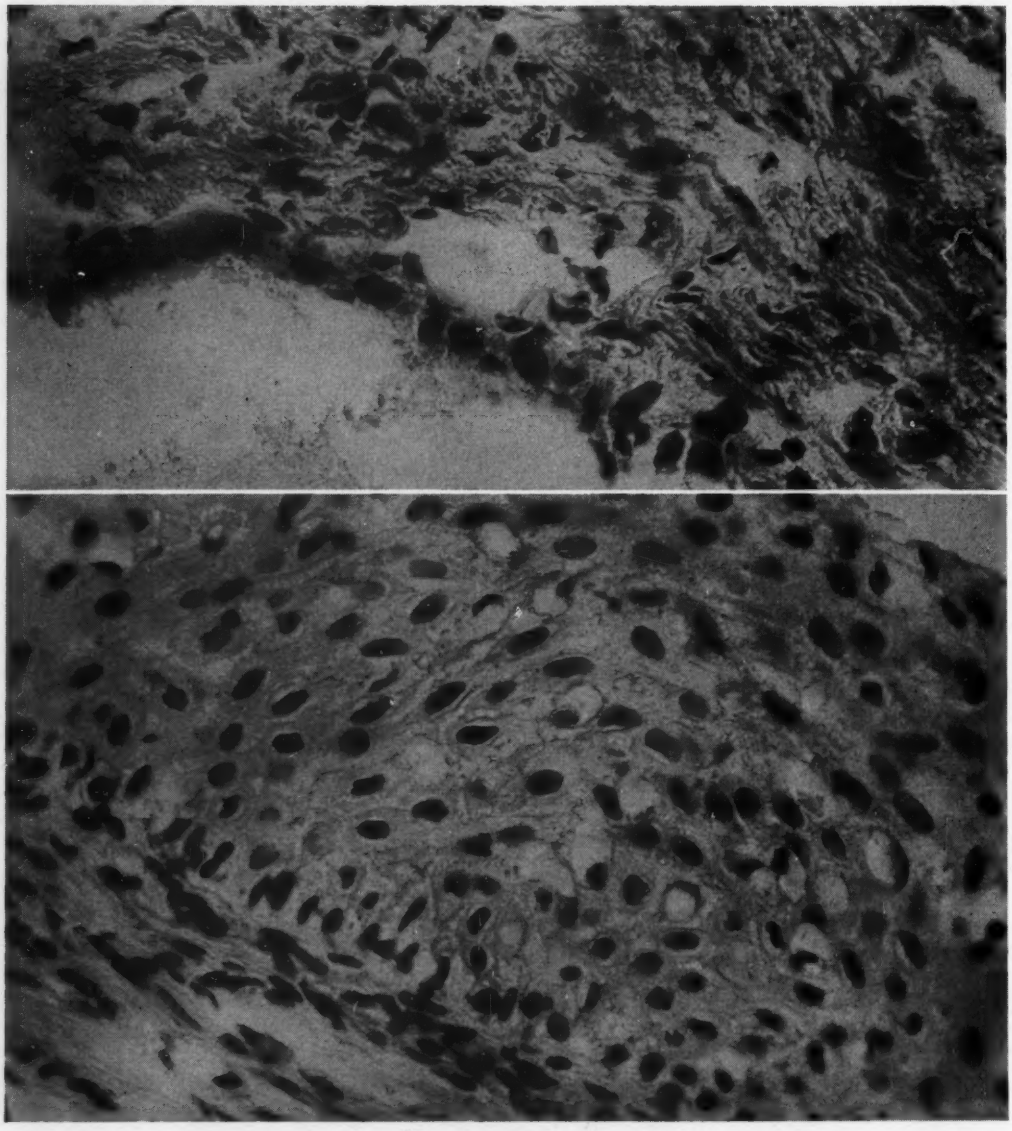


Fig. 9.

Fig. 8.—Higher magnification of epithelium lining small cysts in case of vaginal adenosis. Both cells and contents stained positively with mucicarmine. (×250; reduced ⅝.)

Fig. 9.—Stratification of lining epithelium in vaginal adenosis. (×250; reduced ⅝.)

Primary Adenocarcinoma of the Vagina

The final group of cases consists of 4 primary adenocarcinomas of the vagina, only one of which was seen at Bellevue Hospital, the remainder in the private practice of three physicians. These tumors are exceedingly rare, accounting for less than 10 per cent of the large series of primary carcinomas of the vagina reported by Smith[12] in 1955. It is therefore probable that they constitute less than 0.1 per cent of gynecological malignancy. Three of them belonged to the group recently reported by Novak and associates,[11] and can be suspected of having a mesonephric origin.

CASE 4.—Mrs. E. J., aged 40 years, para 0, gravida 0, was admitted to Bellevue Hospital in June, 1954, complaining of almost constant vaginal bleeding of two years' duration. In 1951 at another hospital she had been subjected to curettage and biopsy because of menorrhagia; in April, 1952, to curettage, biopsy, and myomectomy; in June, 1952, to curettage and biopsy because of intermenstrual bleeding. The latter complaint, despite

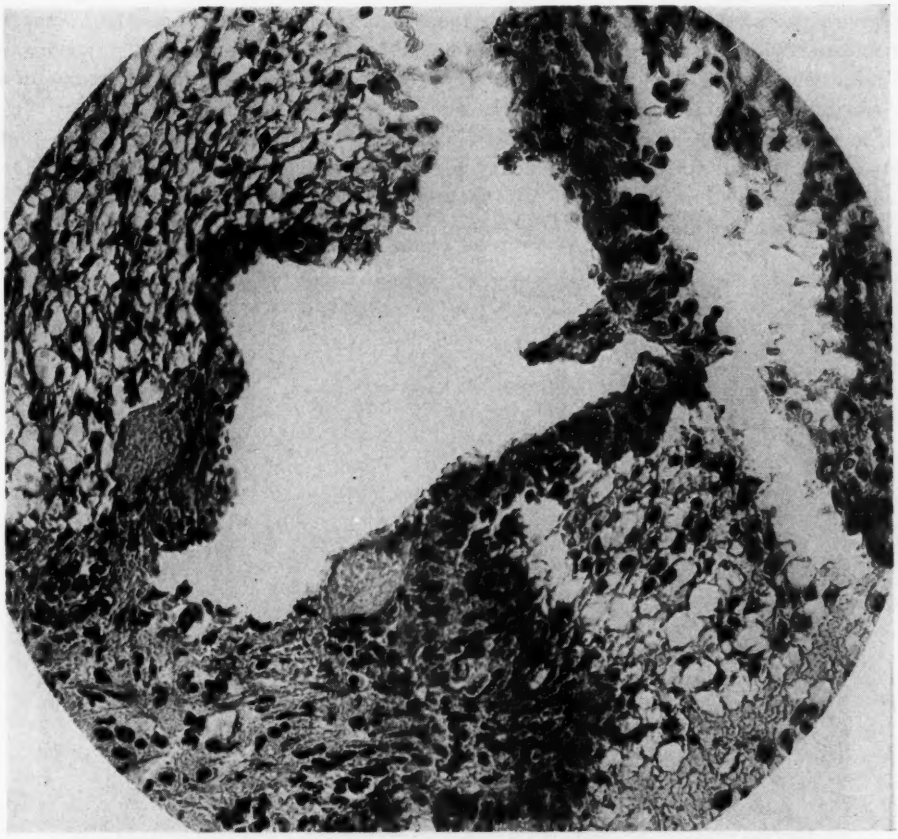


Fig. 10.—Adenocarcinoma of the vagina showing small cells with hyperchromatic nuclei and larger clear cells, believed to be of mesonephric origin. (×200; reduced ⅓.)

these procedures, had continued, together with the development of frequency and urgency up to the time of her admission. General examination was negative. Gynecological examination disclosed a 3 cm. indurated mass with vague borders in the middle third of the anterior vaginal wall. The upper vagina was normal as was the remainder of the examination (Fig. 10). Biopsy revealed that this tumor was composed of irregular glandular acini lined by one or more layers of small cells with deep-staining cytoplasm, the nuclei having neoplastic characteristics. In many areas these cells became continuous with groups and masses of pale vacuolated clear cells with smaller nuclei. Smaller amounts of stroma were present. A diagnosis of adenocarcinoma of the vagina of mesonephric origin was made. Because of the extent and duration of the disease, it was determined to make an attempt at anterior pelvic exenteration. However, on exploration extensive involvement of the pelvic and lower aortic lymph nodes was found and the procedure was abandoned after clips were placed in the region of the involved nodes. Deep x-ray was begun, 1,700 r depth doses being given through ten abdominal and pelvic ports. At the conclusion of this treatment in August the local lesion appeared to have completely regressed. She then received 2,800 mg. hr. of radium from eight 5 mg. tubes in a plastic mold applied to the

anterior vaginal wall. In October of the same year she was readmitted with thickening and induration of the anterior vaginal wall and a large tender lower abdominal mass which was thought to be neoplastic. It was felt that no further treatment should be given and she was discharged to the follow-up clinic. She returned to this clinic at the end of January, 1955, stating that she felt well and had gained weight. Two months before she had experienced a sudden gush of purulent, bloody, foul-smelling discharge from the vagina which had gradually ceased. On examination the abdominal mass had disappeared. The anterior vaginal wall showed moderate scarring and thickening. The cervix, uterus, and adnexa appeared normal except for slight parametrial thickening. Cystoscopy which had constantly revealed normal findings again showed no bladder involvement. In July, 1955, a small recurrence was discovered between the clitoris and the urethra. This was treated with deep x-ray despite the heavy previous dosage. A rather marked reaction followed this therapy but the nodule disappeared and she has remained well since. When she was last seen in June, 1956, no evidence of neoplasm could be found.

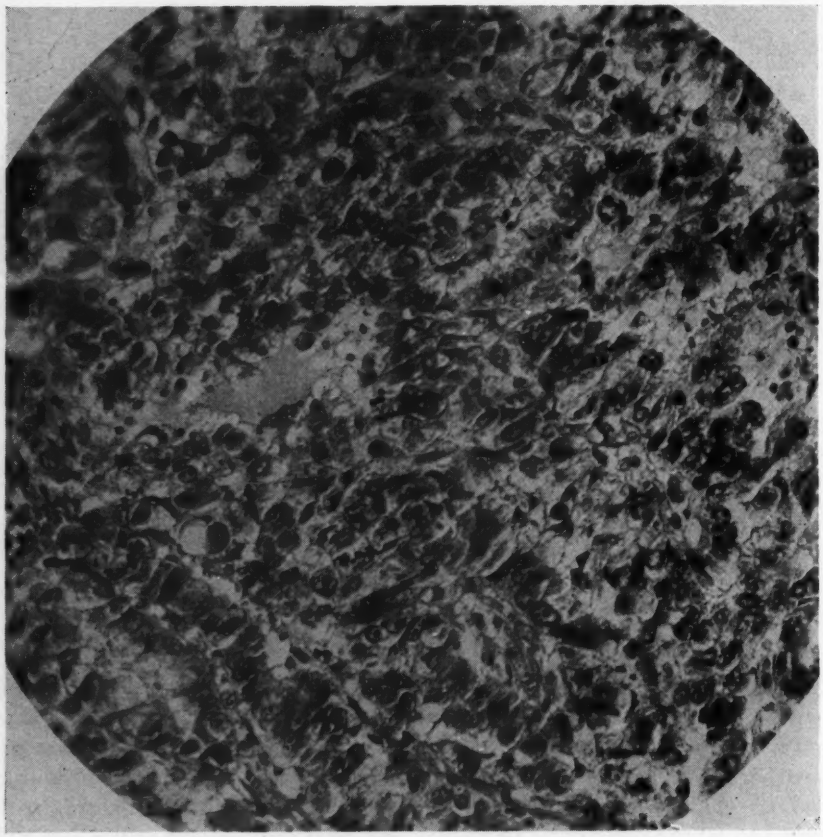


Fig. 11.—Adenocarcinoma of vagina believed to be of mesonephric origin. (×200; reduced ⅙.)

Comment.—This case has many points of interest. In the first place, it emphasizes the inadequacy of our present routine methods of examining the vagina. This is likely to be cursory from the point of view of palpation. In our eagerness to look at the cervix, we insert a bivalve speculum which obscures our inspection of the vagina and we rarely inspect this structure as we withdraw it. Finally, the anterior vaginal wall cannot be properly visualized unless the patient is placed in the knee-chest position. Granted that more careful examination would be a waste of time in most instances, nevertheless, it is

warranted in patients who give a history of constant bloody discharge which does not appear to have a source in the cervix or uterus. Had it been done in this patient an earlier diagnosis might have been made.

Her course has been remarkable. It is far too early to be sure but may not this be one of those rare cases in which a malignant tumor disappears following a severe infection in the area of neoplastic involvement? We will continue to follow her with interest.

CASE 5.*—Miss C. W., aged 16 years, was admitted to the Conemaugh Valley Memorial Hospital in July, 1949, because of continuous bleeding for the past two years. Examination was negative except for pelvic findings which showed a friable mass involving the upper anterior vaginal wall about 3 cm. in diameter. The cervix, corpus, and adnexa appeared normal. Slight lateral parametritis was thought to be present (Fig. 11). Biopsy from the area showed an adenocarcinoma made up of a network of spaces with very little intervening stroma. The lining cells were irregularly shaped but tended to be cuboidal, the nuclei showing all the characteristics of malignancy. In places they were piled up in several layers while in others they formed papillary projections into the central space. The diagnosis was adenocarcinoma of the vagina, probably mesonephric in origin.

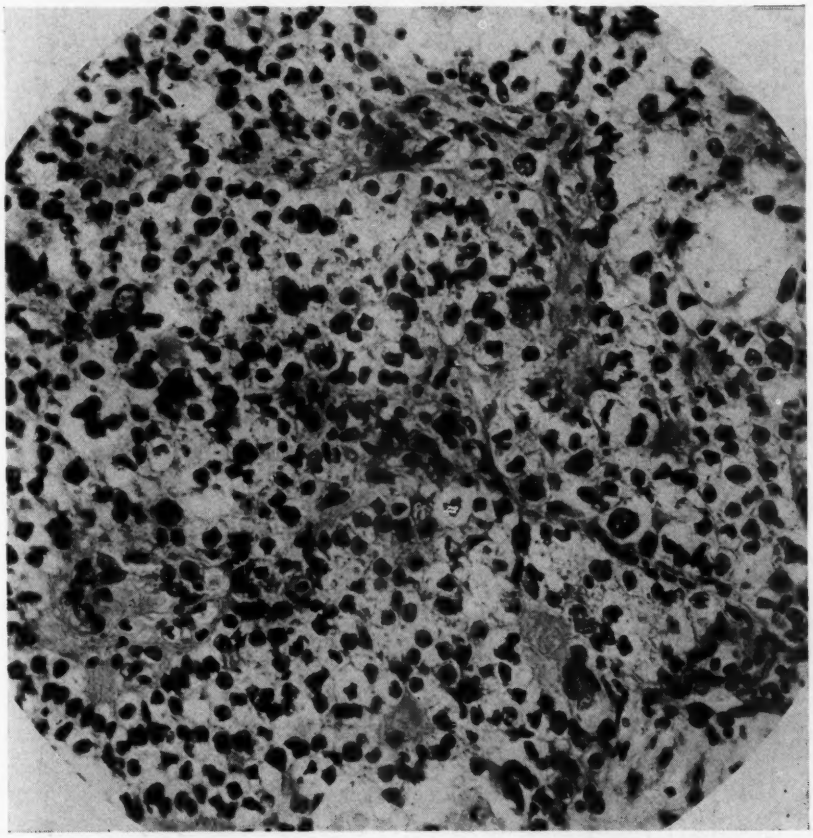
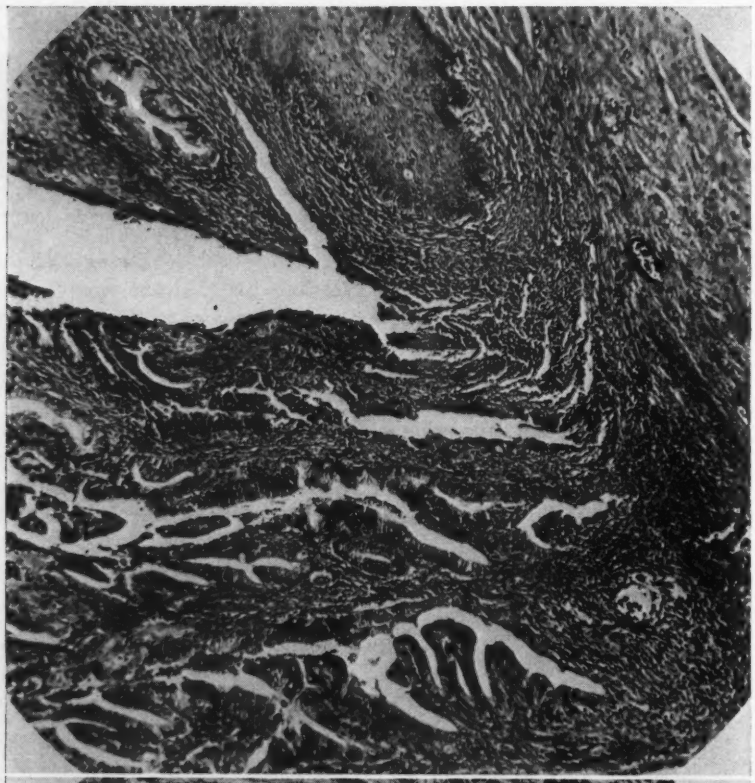


Fig. 12.—Adenocarcinoma of vagina believed to be of mesonephric origin. (×200; reduced ⅙.)

It was decided to attempt surgical excision. After transection and mobilization of the upper third of the vagina, a total hysterectomy and bilateral salpingo-oophorectomy with removal of the upper third of the vagina were carried out. The parametrium adjacent to the uterus was removed, the ureters being identified but not mobilized. No enlarged

*This case is reported through the courtesy of Dr. George Bloom of Johnstown, Pa.

Fig. 13.



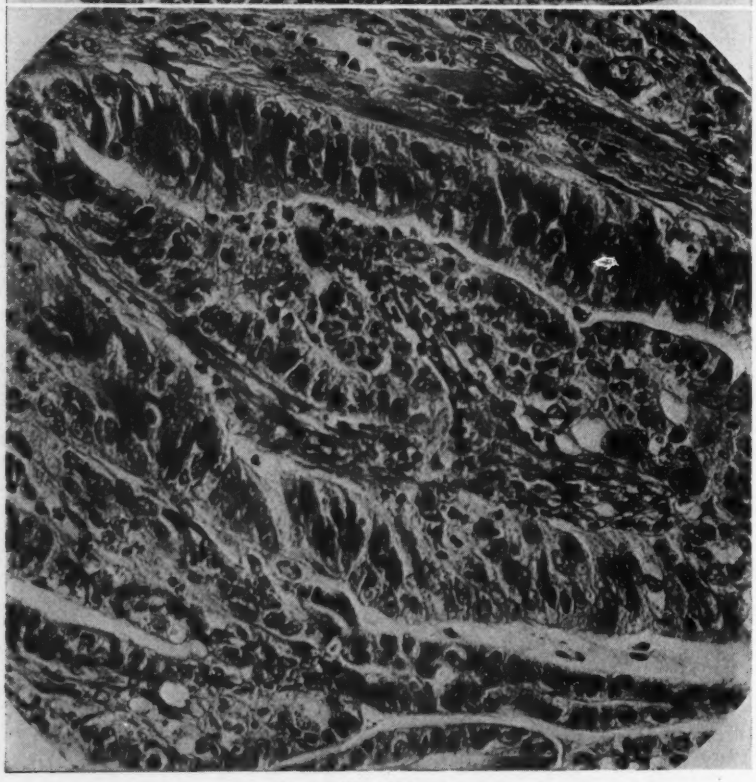


Fig. 14.

Fig. 13.—Papillary adenocarcinoma of vagina believed to be of Müllerian origin. Shows relation to normal mucosa and lack of penetration of underlying vaginal wall. (×45; reduced ⅙.)

Fig. 14.—Higher magnification of papillary adenocarcinoma of vagina. (×200; reduced ⅙.)

lymph nodes were palpated. The excised tumor proved to be superficial and had not penetrated the vaginal wall. The patient received deep x-ray therapy postoperatively, approximately 4,000 r being given through two ports. She has remained well and married in 1951. In October, 1954, examination showed no evidence of neoplasm.

CASE 6.*—Miss R. S., aged 16 years, whose menses began at 11 and had been normal, was admitted to the Lenox Hill Hospital in January, 1952, for the investigation of lower abdominal pain and of a mass that could be palpated anterior to the rectum. On examination under anesthesia there was found to be a yellowish hemorrhagic mass arising from the right anterolateral portion of the upper vagina. It was very superficial and was easily detached. The underlying tissue showed little induration. The cervix and the remainder of the pelvic organs appeared normal.

Microscopic examination (Fig. 12) showed sheets of malignant epithelial cells of varying size with nuclei showing all the characteristics of malignancy and varying greatly in size; in places these cells formed small glands with little or no intervening stroma. Many "clear cells" were present with small nuclei. The diagnosis was adenocarcinoma of the vagina, probably mesonephric in origin. It was first thought to be a metastatic growth and therefore an exploratory operation was carried out. No other primary growth was discovered, the internal pelvic organs were normal, and no evidence of extension of the growth was found. Surgical excision was not considered and the lesion was treated

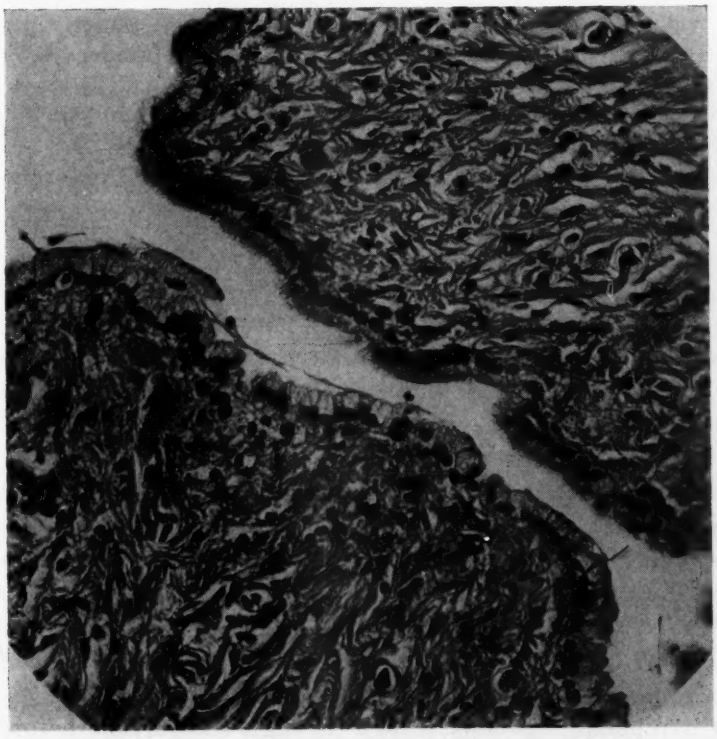


Fig. 15.—High columnar epithelium lining cyst adjacent to but not related to papillary adenocarcinoma. These cells took positive stain with mucicarmine. (×200; reduced ¼.)

with radiation. The site of the lesion received 3,000 mg. hr. while a similar dosage was applied to the uterine cavity. This proved entirely ineffectual and when widespread dissemination became apparent, deep x-ray therapy was given. Later Coley's toxin and massive stilbestrol therapy were attempted. The patient died with widespread metastatic disease in August, 1954.

*Presented through the courtesy of Dr. John Vieta, New York City.

Comment.—These two cases are almost identical except that in Case 6 the tumor was less differentiated. Nevertheless they offer a good comparison. While it is by no means a certainty that the course of the second might have been altered by surgical extirpation, rather strong evidence has been presented by Smith[12] and by Douglas[13] that the latter treatment offers the best chance of permanent cure, particularly when no evidence of distant spread can be discovered.

CASE 7.*—Mrs. B. R., aged 42 years, gravida iii, para ii, was seen in November, 1953, because of continuous bleeding of six months' duration. On examination she was found to have a cauliflower papillary growth whose base was about 4 by 3 cm. on the posterior wall of the vagina at about the junction of the lower with the middle third. The remainder of the pelvic findings were normal. A biopsy was first interpreted as papillary adenoma. The patient was admitted to the Mt. Sinai Hospital in December, where the entire area with the surrounding uninvolved vaginal wall was excised. In mobilization of the upper vagina, a vaginal cyst was encountered which appeared unrelated to the tumor and this was also removed (Figs. 13 and 14). Microscopic examination showed a well-differentiated papillary adenocarcinoma suggesting the type arising in the cervix. It had not penetrated the vaginal wall. The cyst was lined with high columnar epithelium (Fig. 15). In January, 1955, a radium plaque was placed against the posterior wall of the vagina, a total of 2,600 mg. hr. being given. The patient has remained well without evidence of recurrence.

Comment.—This case, in contrast to the others, appears to be a clear-cut Müllerian carcinoma. While not directly related to the vaginal cyst of Müllerian type found accidentally in its vicinity, it appears likely that it arose in a similar vestigial structure. Again this specimen emphasizes the fact that these growths are often limited by the vaginal wall. While it is too early again to feel certain that this patient is cured, it appears highly likely.

Comment

This small collection of cases overemphasizes the prominence of the malignant lesions. The benign lesions are far more frequent. They are generally symptomless except in the case of large solitary cysts or in adenosis which has involved the surface of the vagina. Their removal is a simple matter involving resection of the vaginal wall in which they lie. Diffuse adenosis appears to be the one exception to this statement, since its removal may often be mutilating. While it is true that excision may prevent subsequent malignant transformation, it must be pointed out that adenocarcinoma is very rare. Furthermore, the suspicion has been voiced that many hidden adenomatous lesions of both Müllerian and mesonephric origin are impossible to detect clinically. From the point of view of prophylaxis, the removal of recognizable benign lesions is not likely to be efficient as a preventive measure. It is believed that conservatism is fully justified in caring for benign lesions, provided they are symptomless. When carcinoma does develop from such an intramural lesion, its onset is probably much more insidious than is that of the more common epidermoid carcinoma. It must break through the surface before the initial symptom of bleeding takes place. The problem of early diagnosis is consequently greater.

Summary and Conclusions

The embryological basis for the presence of cystic or glandular elements in the vaginal wall has been reviewed. A clinical classification of these lesions

*This case is reported through the courtesy of Dr. Joseph Gaines of New York City.

has been suggested. A group of cases has been reported which illustrates these uncommon or rare lesions.

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Discussion

DR. RALPH A. REIS, Chicago, Ill.—Dr. Studdiford has given us a good working classification of adenomatous lesions based on origin, and with this classification we would agree even though we prefer the term paramesonephric to Müllerian.

We do not agree, however, that the epithelioma is the commonest vaginal tumor. We have encountered many more vaginal cysts of mesonephric or paramesonephric origin. Like Dr. Studdiford, we feel that these two duct remnants persist more frequently than is realized and that if looked for carefully they would be found in 1 to 2 per cent of cases, as was done by Huffman in our laboratory.

Excellent studies of mesonephric and paramesonephric cysts and tumors of the broad ligaments by Gardner, Greene, and Peckham also have come out of our institution, and it is on their recommendation that we have dropped the welter of proper names attached to such lesions and are classifying all on the basis of origin, i.e., mesonephric and paramesonephric. They have shown that differentiation between the two is relatively simple, being based on differences in cell size and nuclear size plus the failure of mesonephric epithelium to respond to cyclic hormone stimulation as does paramesonephric epithelium. The location of such a lesion is not indicative of its origin.

Dr. Studdiford has stated that the terminal portion of the mesonephric duct always ends at the level of the hymen. Termination of the duct at this level is not universal, for less than 2 months ago we removed such a lesion from the lower end of the labium majus well below the level of the hymen where its subcutaneous position was a source of continuing annoyance to the patient. We agree that solitary cysts without symptoms need not be removed.

We feel the same concerning vaginal endometriosis. We control our curiosity and leave the symptomless lesion undisturbed but under continuing observation. We have not encountered vaginal adenosis. Nor have we been as fortunate in our results with adenocarcinoma of the vagina, for we have achieved no five-year cures.

Finally, Dr. Studdiford has emphasized the need for careful routine inspection of the vaginal mucosa, particularly in all instances of abnormal bleeding. With this we agree wholeheartedly. For the carrying out of this well-advised procedure, we would recommend careful routine vaginal inspection and palpation as an initial part of every pelvic examination.

DR. J. MASON HUNDLEY, JR., Baltimore, Md.—As we all know, the normal vagina is devoid of glandular elements and when present these are the vestigial remains of the mesonephric duct, or Wolffian duct. We all agree with Dr. George Gardner and his group

that such eponyms should be abolished and that the anatomical name should be used. However, these terms have become deeply entrenched and it will take time for their eradication.

Robert Meyer was one of the first to record the findings of vestigial elements of the mesonephros in the region of the cervix in a high percentage of embryos examined. As would be expected, the incidence of these elements markedly diminishes as the fetus reaches maturity, for they are not present in the normal adult vagina. When the fetus has reached the 5 mm. stage there is a beginning of degeneration of the mesonephros. In early fetal life the mesonephric duct begins in the mesovarium, passes downward in the parametrium close to the uterine body, then enters the cervical region where there is found an ampullary enlargement. The duct may leave vestigial remains anywhere in its course; especially are they found in the parametrium, cervix, and vagina. They may also be found near the ovary and be the source of the tumors spoken of as mesonephromas by Schiller and others. Gruenwald has shown that interruption in the development of the mesonephronic duct will prevent the growth of the paramesonephric duct beyond the point of interruption (quoted from Curtis and Huffman).

Lesions of endometriotic origin may be seen in the posterior fornix and appear like small mulberries; these are usually secondary to similar lesions in the pelvis but may be primary. In the lateral vaginal fornices growths may be seen that originate from mesonephric remnants, as described by Novak and Woodruff. These lesions may be papillomatous and either benign or malignant. Other rare lesions, as described by the same authors, are the probable mesonephric lesions which are papillomatous and grapelike in appearance. They simulate the sarcoma botryoides which occurs in infants and may originate from the mesonephric rests. According to Novak, the role of the Müllerian or paramesonephric system as a source of vestigial elements for potential tumor growth is debatable (personal communication).

Metastatic carcinoma to the vaginal vault, from corpus carcinoma, is a fairly common observation; however, primary adenocarcinoma is, with us, a rarity. The presence of granulation tissue in the vault after panhysterectomy for carcinoma is a very common occurrence. A biopsy is imperative to rule out malignant recurrence. We have only one case of primary carcinoma of the vagina to report. The details are as follows:

The patient, 35 years of age, was referred to me by a colleague, Dr. Bessie Moses, in 1933, with the complaint of vaginal bleeding of five months' duration. At first there was slight spotting and later this became more profuse. The pelvic examination was entirely normal except on the floor of the vagina, just within the hymen, where an area about 1 cm. in diameter was seen which had an indurated base and was slightly papillomatous. The rectal examination showed no apparent mucosal involvement. The lesion somewhat resembled a chancre in appearance but this was ruled out by a negative dark-field examination and the Wassermann test was negative. A biopsy showed a typical adenocarcinoma. This diagnosis was confirmed by Dr. Emil Novak and others. The growth was radiated with heavy filtration and excellent regression ensued. Inguinal glands were never palpable. Eight weeks following irradiation there was no semblance of growth noted. The tissues of the perineal body and vaginal septum were soft and pliable although somewhat whiter in color. Frequent follow-up examinations were made over a period of 23 years, the last being in October, 1952. The patient is now living in New Zealand and reports she is well and has no symptoms. I believe that radical surgery with excision of the entire vagina would be the present-day procedure of choice.

RESULTS OF TREATMENT OF PRIMARY OVARIAN MALIGNANCY*

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THIS is a report of 336 cases of primary ovarian malignancy treated at the Toronto General Hospital and the Ontario Institute of Radio-Therapy from 1936 to 1952, inclusive. The clinical histories have been reviewed and for those patients who have survived 5 years or longer the pathological slides have been restudied.

Pathology

The restudy of the pathological diagnoses was undertaken primarily to exclude papillary tumors of doubtful histological malignancy. The wide variation reported in 5 year survival for malignant ovarian tumors,[1] in part at least, may be explained by the inclusion or exclusion of tumors of this group.[2, 3] Only 3 papillary tumors of equivocal histological maligancy have been included in the series. In each of these, papillary growths on the surface of the tumor and pelvic peritoneum were evident. Of the 3 patients, one died of carcinomatosis of the abdomen in 15 years, one has been alive and well for 9 years, and one developed a pelvic recurrence in 3 years which was surgically removed and the patient has remained well for 14 years. The long survival of these 3 patients emphasizes the relatively favorable prognosis in papillary ovarian tumors of equivocal histological malignancy despite extension through the tumor capsule.

Among the pseudomucinous group of tumors there were 6 cases associated with pseudomyxoma peritonei. Only 2 of 6 neoplasms were histologically malignant and both these patients died within 2 years. The remaining 4 patients all eventually died from the disease, living 1, 5, 8, and 18 years. As these tumors were histologically benign, they are not included in the statistical summary of survival.

Bilateral ovarian involvement was frequently encountered, particularly in the papillary group of neoplasms, and in most instances this appeared to be secondary spread from the primary tumor. In 19 cases, however, the bilateral tumors were considered to be separate primary growths. This diagnosis was based on freely movable tumors which presented no gross or microscopic evidence of extension through the capsule of either neoplasm. Only 4 of the 19 patients lived 5 years or longer. This poor survival rate suggests that the assumption of two primary tumors may have been incorrect and that one resulted from lymphatic spread from the original neoplasm.

There were 2 solid malignant teratomatous tumors. Both were freely movable, unilateral, and surgical removal appeared to have been complete. Both patients were 20 years of age and died within 2 years.

There were 31 tumors belonging to the dysontogenetic group of neoplasms: 20 granulosa-cell tumors, 9 dysgerminomas, and 2 arrhenoblastomas. Most

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of these have been previously reported.[4] Due to their rather special pathological characteristics and their supposed low-grade clinical malignancy, the survival rate for this group is shown separately.

The remaining neoplasms were made up of malignant papillary cystic tumors, papillary solid tumors, solid adenocarcinoma, and malignant pseudomucinous neoplasms.

Clinical Features

The review of the clinical histories served mainly to emphasize the silent nature of ovarian malignancy until the disease is far advanced and beyond the hope of surgical cure. The three common complaints were an enlarging abdomen, an abdominal mass, and vague lower abdominal pain or discomfort. Approximately 10 per cent of the patients, excluding those with granulosa-cell neoplasms, complained of vaginal bleeding. The duration of these symptoms bore no evident relationship to the extent of the disease as determined at laparotomy. The hope for early diagnosis appears to rest on the chance discovery of ovarian enlargement by repeated bimanual examinations at intervals of not more than 6 months. The impracticability of this applied to a large number of patients is self-evident.

The cases were clinically classified according to the extent of the disease as determined at laparotomy. They were divided into 4 groups as shown in Table I.

TABLE I. CLASSIFICATION

Group I.	Complete removal of the primary tumor with no gross or microscopic evidence of extension beyond tumor capsule.
Group II.	Complete removal of primary tumor and all evident secondary tumor.
Group III.	Complete or partial removal of the primary tumor with incomplete removal of secondaries.
Group IV.	Inoperable with biopsy only.

To simplify the statistical presentation of the cases, Groups I and II were classified as favorable for surgical cure and III and IV as unfavorable. There were 110 favorable and 195 unfavorable cases.

The preponderance of unfavorable cases is the most discouraging aspect of ovarian malignancy. The survival rate for all cases except those of the dysontogenetic group is shown in Table II.

TABLE II. SURVIVAL RATE IN TOTAL SERIES OF 305 CASES

DURATION	NO. OF CASES	NO. ALIVE	%
3 years	305	82	26.8
5 years	265	48	18.1
10 years	147	20	13.5

This low survival rate is similar to that reported by Randall[5] and Taylor[6] but not as high as that reported by Kerr and Elkins[7] or Counseller.[8]

The results obtained in the favorable cases are presented in Table III.

TABLE III. SURVIVAL RATE IN SERIES OF 110 FAVORABLE CASES

DURATION	NO. OF CASES	NO. ALIVE	%
3 years	110	51	46.3
5 years	102	35	34.2
10 years	48	16	33.0

The less than 50 per cent survival in this group is disappointing. Practically all patients received postoperative high-voltage therapy. The initial surgical procedures employed in the favorable cases are shown in Table IV.

TABLE IV. SURVIVAL RATES IN RELATION TO TYPE OF SURGICAL TREATMENT IN FAVORABLE CASES

OPERATION	NO. OF CASES	3 YEAR SURVIVAL	%
Oophorectomy	27	9 cases	33.3
Bilateral oophorectomy	26	10 cases	37.2
Bilateral oophorectomy and hysterectomy	57	30 cases	52.6

It was disappointing to find bilateral oophorectomy and hysterectomy employed in only about half of the favorable cases when it offers the best hope of survival. From a review of the histories of these cases it appeared that failure to recognize the tumor as malignant was the reason for not employing radical surgery in all cases. If doubt is present in regard to the malignancy of any ovarian tumor at the time of laparotomy, frozen section of the neoplasm should be employed rather than trusting to an opinion based on gross examination alone.

The survival rate for the unfavorable cases is presented in Table V.

TABLE V. SURVIVAL RATE IN 195 UNFAVORABLE CASES

SURVIVAL	NO. OF CASES	NO. ALIVE	%
3 years	195	31	15.3
5 years	163	13	7.0
10 years	99	4	4.0

It is surprising that even this small number of patients lived 5 years or longer. All patients received postoperative high-voltage therapy which in many cases was repeated. The unexpected survival rate may be due to other factors but it seems reasonable to attribute most of the credit for survival to this therapy.

The follow-up record for the group of dysontogenetic neoplasms is shown in Table VI.

TABLE VI. SURVIVAL RATE IN GROUP OF DYSONTOGENETIC NEOPLASMS

		NO. OF CASES
Granulosa-cell tumors		20
Alive and well 4-15 years	9	
Dead	9	
Dead from other causes	2	
Dysgerminoma		9
Alive and well 4, 6, 8, and 14 years	4	
Dead 1-3 years	5	
Arrhenoblastoma		2
Alive and well 4 and 9 years	2	

Our experience with tumors of this group suggests they have greater malignant potentialities than is generally supposed. Late recurrence of the granulosa-cell tumor was common, 3 recurred after 5 years and 2 after 10 years. In contrast to this the dysgerminoma recurred early with all deaths taking place within three years. Recently Mueller and associates[9] reported 7

cases and collected information from the literature on an additional 420 cases of dysgerminoma. From this they report a 5 year survival rate of only 27 per cent.

Radiotherapy

It was difficult to assess the value of high-voltage x-ray therapy. Practically all patients received it and we therefore have no controls for comparison. In the favorable group of cases the 5 year survival rate was only 34.2 per cent despite the employment of postoperative radiotherapy in almost all cases. On the other hand, 7 per cent of the patients in the unfavorable group have remained alive for 5 years. It is our opinion that in some cases radiotherapy retards the rate of tumor growth and the formation of ascitic fluid. Occasionally secondary tumor masses in the pelvis temporarily disappear or are reduced in size. Two cases that were considered inoperable at initial laparotomy became operable after the administration of high-voltage therapy. Both patients lived over 5 years, one without evident malignant disease, the other with a fixed pelvic mass. It appeared that the cystic papillary adenocarcinoma was more likely to respond favorably than the solid adenocarcinoma and that the pseudomucinous carcinoma was particularly radioresistant. Both the granulosa-cell tumor and the dysgerminoma are generally considered radiosensitive neoplasms but this has not been so in our experience in the few cases we have treated.

Our experience with radioactive gold in carcinoma of the ovary is too limited to form an opinion of its value. Miller[10] recently reported on 101 cases of malignant effusions treated at the Ontario Institute of Radio-Therapy. Twenty-one of these were due to carcinoma of the ovary. The results were disappointing. The treatment in all cases was undertaken purely as a palliative measure largely to inhibit the formation of ascitic fluid. The employment of radioactive gold in the favorable case as suggested by Keettel and Elkins[11] may prove of greater value than routine postoperative high-voltage x-ray. Depth penetration is slight, however, and effective radiation is limited to about 6 mm. It is evident therefore that gross secondary tumor will remain relatively unaffected by the therapy. Its value theoretically appears to lie in the treatment of the favorable case in which the tumor has been ruptured during removal or minute unrecognized surface implants are present.

Summary

This review of 336 cases of ovarian malignancy shows a 5 year survival rate of only 18.1 per cent. The preponderance of advanced cases is partly responsible for this but even in the cases judged favorable for surgical cure only 34.2 per cent of the patients lived for 5 years. The best results were obtained in patients treated by bilateral oophorectomy and hysterectomy. The over-all poor results occurred despite the employment of postoperative high-voltage treatment in practically all cases. The use of intraperitoneal radioactive gold in the favorable cases, either alone or as an adjunct to high-voltage treatment, offers a possible means of improving the survival rate.

The clinical picture of ovarian malignancy is a depressing one. Unless some new successful treatment is evolved or some new procedure leading to early diagnosis is discovered, there appears to be no ground for optimism in the treatment of this disease.

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Discussion

DR. WALTER L. THOMAS, Durham, N. C.—Five years ago we sat in this hall and listened to a discussion of Dr. Clyde Randall and Dr. Donald Hall's presentation on their results of treatment of ovarian malignancies. Have we made any real progress in five years? Are the patients reporting earlier? Certainly in our experience the patients are reporting just as late as they did in 1951.

The insidious nature of the lesion makes a primary surgical cure almost impossible. Dr. Henderson and Dr. Bean have shown a five-year survival rate of only 34 per cent in the most favorable group. Seventy-five per cent of our patients fall into the unfavorable group.

It seems to me that we must search for another method of attack upon "this silent killer." I have an idea that the weapon could be some carcinolytic or cytotoxic chemical or chemicals. Recent clinical trials with oral nitrogen mustards have encouraged us. May I recite in some detail the story of one of our patients. The result so far has been miraculous.

The patient was a 49-year-old white married para i, admitted to the thoracic surgical division on Sept. 18, 1955, with a chief complaint of "shortness of breath" of one month's duration. She had been in her local hospital for three weeks where four thoracenteses had been done on the right chest for a pleural effusion. A fifth thoracentesis was done on September 19 with the removal of 900 c.c. of amber fluid. A diagnostic bronchoscopic examination on September 20 was negative. Cytological smears on the pleural effusion sediment were reported as Type IV (adenocarcinoma), on the bronchial washings, Type II.

A celiotomy was performed on September 23. Exploration after aspiration of about 2,500 c.c. of ascitic fluid revealed large 15 cm. bilateral fixed ovarian cystic masses. There were numerous implants varying from a few millimeters to 1.5 cm. scattered throughout the peritoneal cavity, large 2 to 4 cm. implants in the greater omentum. There were no palpable nodules in the liver but palpable implants were felt beneath the right diaphragm. Loops of small bowel were adherent to the upper portions of the pelvic tumor masses. There were implants on these loops and on other surfaces of both small and large bowel. It was concluded that the pelvic masses with the extensive peritoneal spread were irremovable. Biopsies of the left ovarian mass and a peritoneal implant were obtained. The pathologist reported undifferentiated carcinoma.

Chemotherapy under the supervision of our hematologist was instituted on September 26. She was first given oral triethylenemelamine (TEM), 2.5 mg. daily for three days. She was discharged on October 2 to continue TEM every five days preceded by a leukocyte count. During the next seven months she felt well and carried on her usual duties. In February, 1956, because of the development of a leukopenia and thrombocytopenia, Chlorambucil (CB 1348), another water-soluble aromatic nitrogen mustard, was substituted for TEM.

Within two months after the institution of chemotherapy there was noted a regression in the size of the pelvic tumor masses; the hydrothorax and ascites did not recur. The masses were no longer palpable by abdominal examination and the pelvic viscera were

movable by the fourth month. The fifth month revealed no fixation and we now considered her condition favorable for reoperation. It took us two months to convince the hematologist that we could now remove the primary tumors and that this was most advisable.

The abdomen was entered without difficulty on March 30, 1956. There were no ascites, no adhesions. Careful inspection disclosed no omental implants and only a few parietal and visceral implants. The right ovary was about normal in size and movable—the left ovarian mass was 5 cm. in diameter and adherent—there was a moderate amount of necrotic tissue surrounding the left ovarian mass and in the cul-de-sac.

A bilateral salpingo-oophorectomy, complete abdominal hysterectomy, complete omentectomy, and appendectomy were easily performed. The cytologist reported a smear made directly from the left ovarian specimen Type V with the statement that the effects of nitrogen mustard resembled those of irradiation but that there were many active-appearing cells still present. The final microscopic report was papillary serous cystadenocarcinoma of both ovaries, bilateral chronic salpingitis, chronic cervicitis, atrophic endometrium, no tumor being seen in the omentum or appendix. She was discharged on April 8 and has been followed regularly since then. The CB 1348 has been continued at 2 mg. daily or every other day depending upon her leukocyte count. Her last check was on August 21. She has been completely asymptomatic save for some spontaneous bruising over the arms and legs—no external or mucous membrane bleeding. The chest, the abdomen, and the pelvis remain clear. She is very happy and so are we.

We sincerely hope that five years from now we can report on her that all goes well. We have not decided as yet just how long we shall continue the nitrogen mustard therapy.

The results of our ovarian carcinoma therapy have left me very pessimistic in the past. There may be on the horizon a new and more successful attack upon this dread disease.

DR. ROBERT A. KIMBROUGH, Philadelphia, Pa.—Dr. Henderson's results are comparable to those reported by other recent authors. Even in the most favorable group the ten-year survival is only 33 per cent. The insidious, symptomless nature of ovarian carcinoma permits wide dissemination in more than two-thirds of cases before patients present themselves for treatment. Another discouraging feature is the rapidity of its development. All of us have had occasional patients with hopelessly extensive ovarian carcinoma who only a few months previously were found to have no pelvic abnormalities. In the effort to make earlier diagnoses we advocate routine pelvic examination at intervals of six months rather than the usually advised yearly intervals.

We have found frozen section examination to be of very limited value in reaching a conclusive diagnosis at the time of operation. Even with the best paraffin sections the decision between malignancy and benignancy poses one of our most difficult problems. The choice of the type of operation to be employed in older patients is easy. In younger patients with doubtful tumors we prefer to perform a conservative procedure and await paraffin sections. In the event of malignancy of the tumor, reoperation becomes imperative in most instances.

We agree with the essayist on the value of radiation therapy in even apparently hopeless cases. While the results are usually poor, an occasional patient becomes a long-time survivor. While our experience with radioactive gold is too recent and too limited to permit its evaluation at this time, we are encouraged to believe that this modality has much to offer.

DR. FRANK R. SMITH, New York, N. Y.—While we are groping for some better method than the ones used at present against this disease, we should emphasize the so-called "second look." We should not wait until the patient has the symptoms of a recurrence but should reoperate on all patients who have been operated upon for cancer of the ovary while they are still symptom free. There are certain patients who live five years, quite happy in their security of having been operated upon, when suddenly a new group of symptoms appears that seem almost like a new tumor. It is usually then too

late for more than palliative therapy or terminal care. I realize it is hard to persuade the patient of the need for a second exploratory operation when she feels well, but I believe it is the only way we can eliminate asymptomatic recurrences.

DR. HENDERSON (Closing).—We had in the group only two proved cases of secondary carcinoma of the endometrium from the primary in the ovary. In the majority of instances, however, we did not have the uterus available for histological examination. My own interpretation of this 10 per cent bleeding was that it could well have been due to secondary carcinoma of the endometrium in more advanced cases.

The early diagnosis of ovarian malignancy seems nearly hopeless. We had 4 patients—2 who had had the abdomen opened only two years before the discovery of advanced carcinoma, and 2 who had been examined under anesthetic at the time of vaginal plastic repair eight months before the discovery of ovarian carcinoma. A chance discovery of an early lesion by repeated examinations at six-month intervals might lead to the discovery of some early cases.

Dr. Kimbrough states that he has had poor results from the use of frozen sections. In some cases, however, a positive diagnosis can be made by this procedure when, on gross examination of the tumor, the surgeon does not feel sure of the malignancy. We have found that, when unilateral oophorectomy has been performed, if the tumor is subsequently reported as malignant, the surgeon is reluctant to advise a second operation. Nevertheless, these patients should have a second operation.

OXYGEN STUDIES OF THE CORD BLOOD OF CESAREAN-BORN INFANTS*

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THE problem of asphyxia neonatorum is a complex one and has numerous aspects. Perfect initiation of respiration involves: (1) a normal medullary response at the time of birth, and (2) intact and unobstructed respiratory passages. Medullary response in the newborn may be interfered with by the dulling action of drugs, by the trauma of labor, or by interference with cord circulation. The respiratory passages may be obstructed occasionally by anatomical anomalies, but much more frequently by aspiration of blood, meconium, vernix, and amniotic fluid, or a combination of these materials.

Inasmuch as several of these factors are usually involved, it is difficult in individual instances to evaluate accurately the responsibility of each one in a given case of asphyxia. From a practical standpoint, it is our duty as obstetricians to conduct our deliveries with a minimum of depressing drugs, with the least possible trauma of labor, and with meticulous clearing of the air passages at the time of birth.

Some time ago we selected for study the oxygenation of the arterial blood of the newborn at the time of birth as an important facet of this complicated problem. Throughout these studies the gasometric method of Van Slyke was used which, despite its tediousness, is probably the most accurate method. In the interest of uniformity of results, all of the laboratory work was done by one of us (R. M.).

Our earlier studies[1, 2] showed that spontaneous delivery under light anesthesia gave an average oxygen saturation of 58.8 volumes per cent, while under spinal anesthesia the saturation was 37.8 per cent (Table I). However, if we delete 2 of these where delivery was delayed after the anesthetic was given and one in which there was a tightly coiled cord around the neck, the oxygen saturation under spinal anesthesia averaged 56 per cent. Our best results were in the cases of delivery with outlet forceps. Here the oxygen saturation was 64.8 per cent under general anesthesia, 58 per cent under spinal, and 61.6 per cent under caudal anesthesia. In the more complicated types of delivery, the oxygenation of the infant was decreased in proportion to the difficulty of the operation. In 10 cases with delivery by cesarean section, however, the average was found to be 46.3 per cent of saturation and it was at this point that we decided to continue our investigations.

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TABLE I. AVERAGE OXYGEN SATURATION IN VARIOUS METHODS OF DELIVERY

METHOD OF DELIVERY	NO. OF CASES	GENERAL ANESTHESIA (VOL. %)	NO. OF CASES	SPINAL ANESTHESIA (VOL. %)	NO. OF CASES	CAUDAL ANESTHESIA (VOL. %)
Spontaneous	13	58.8	6	37.8	–	–
Forceps	13	64.8	29	58	11	61.6
Midforceps	5	53.8	21	56.5	–	–
Breech extraction	4	63.6	2	58.2	–	–
Version and extraction	0	–	2	38	–	–
Cesarean section (10 cases)	1	70.3 (Cyclopropane)	9	43.7	–	–

Our work was also prompted by reports that there is an appreciably higher infant mortality rate in abdominal delivery than one would expect if this method is without fetal hazard. We have done determinations on 100 additional infants born by cesarean section and have analyzed our findings. Our cases were all taken from the period between Feb. 1, 1955, and July 1, 1956. They are not consecutive cases and unfortunately some of our more serious complications were not recorded because they happened at night or on week ends when our investigative help was unobtainable.

During this time there was a total of 166 cesarean sections done, with 170 babies delivered, including 4 sets of twins. Thirteen were stillborn or died during the hospital stay, a gross mortality rate of 7.6 per cent. Our section rate during this time was 3.5 per cent. Five babies died as the result of abruptio placentae and 3 of erythroblastosis, including one set of twins (Rh incompatibility was not the indication for the operation). After section for placenta previa, 3 babies died, including one set of twins. Another baby died because the mother was operated upon before term for advanced mediastinal cancer and the last baby was born by section because of a compound presentation. We are not discussing the indications for section, but wish to call attention to the fact that 10 of these 13 babies weighed under 5 pounds, 4 ounces, at the time of delivery. There were 3 deaths of mature infants, one due to erythroblastosis, one to placenta previa, and one to abruptio placentae.

Litchfield and his co-workers[3] in 1951 reported a gross mortality rate of 5.56 per cent, but considered that only 0.83 per cent of the deaths were due to the operation. They believed that aspiration pneumonitis and atelectasis were due to the condition for which the section was done and not to the operation. We cannot, from our experience, agree with this statement. Landesman,[5] in 1951, reported fetal mortality rates in abdominal deliveries varying from 4.9 to 10.8 per cent in our best maternity hospitals. In 1953 he[4] stated that the death rate in cesarean-born infants at the New York Lying-In Hospital had dropped from 7.7 per cent in his previous review, to 5.3 per cent in the years 1950-1952. He commented that there is no added risk to the infant abdominally delivered. This is a conclusion to which we also take exception. Little[6] pointed out the value of the newer concepts of fetal resuscitation, including the use of gastric insufflation of oxygen, the use of phrenic stimulation, aspiration of the stomach and trachea, and the use of detergent alcohol in Alevaire mist. He stressed the importance of the cooperation of the obstetrician, the anesthesiologist, and the pediatrician. He also suggested that the mild respiratory depression of sedation may prevent aspiration. This is the statement of a pediatrician and it shows concern about the fate of the cesarean newborn.

Mack[7] reported that the infant death rate in Detroit from 1947 to 1950 was 65 per 1,000 live births following cesarean section and only 23 per 1,000

live births after vaginal delivery. Considering only elective section uncomplicated by intercurrent disease, the mortality was still 31 per 1,000 live births. These are city-wide statistics and not those from a selected group of operators such as those reported by Litchfield and Landesman.

First, from the diagnostic standpoint, we selected categories that might interfere with oxygenation (Table II). It was assumed that all elective and repeat sections and those for cephalopelvic disproportion with the patient not in labor should give the highest oxygen values. In this series there were 82 such babies and the median oxygen saturation was 53 per cent. These were the highest values in the 100 cases but it was well below those found in simple vaginal deliveries. In 5 erythroblastotic babies the same results were obtained. In toxemia and placenta previa, the saturation was lower still and, as expected, the lowest readings were obtained in 6 cases of placental separation.

TABLE II. OXYGEN CONTENT AND OXYGEN SATURATION IN INFANTS DELIVERED BY CESAREAN SECTION ACCORDING TO DIAGNOSIS

DIAGNOSIS	NO. OF CASES	MEDIAN OXYGEN SATURATION (%)	RANGE	MEDIAN OXYGEN CONCENTRATION (VOL. %)	RANGE
No added risk	81 (82 babies)	53	10.4-95.6	10.7	2.3-19.1
Erythroblastosis	4 (5 babies)	53	18.9-87.1	8.9	3 -14.7
Toxemia	4 (5 babies)	47.5	18.8-76.2	8.8	4 -14.5
Placenta previa	5	48.6	22.5-74.8	9.2	4 -14.5
Separation of placenta	6	33	10.2-55.8	7.2	2.1-12.3

Disregarding diagnosis, the clinical condition of the 103 babies born by section (Table III) was as follows: 72 were in good condition; 18 were mildly asphyxiated and 10 were severely asphyxiated; 2 died after delivery. (These were twins with severe erythroblastosis, the mother of whom had an absolutely contracted pelvis and had had 5 previous sections. She went into labor at 6½ months and was operated upon.) One baby was stillborn after complete separation of the placenta.

TABLE III. CONDITION OF BABIES AT TIME OF DELIVERY

In good condition	72	(2 sets of twins)
Mild asphyxia	18	
Severe asphyxia	10	
Died	2	(erythroblastotic twins)
Stillborn	1	(complete separation of placenta)

This percentage of asphyxia is high in comparison with that associated with normal deliveries. In a previous study,[8] we found that the percentage of asphyxiated babies delivered from below was 9 per cent under general anesthesia and 3.7 per cent under local anesthesia, despite the fact that larger doses of analgesic drugs were used than is now customary. Realizing the danger of asphyxia in cesarean-born babies before this study began, we followed a technique in handling the cesarean newborn which will be described later.

Our studies showed that the oxygen capacity of the cesarean newborn infants varies considerably in its range but is not in itself a cause of asphyxia (Table IV). The median oxygen saturation is decreased, however, when the

TABLE IV. CONDITION OF BABIES ACCORDING TO OXYGEN CAPACITY (HEMOGLOBIN OF CHILD) OXYGEN SATURATION, AND OXYGEN CONCENTRATION

CONDITION OF BABY	NO. OF CASES	OXYGEN CAPACITY (MEDIAN VOL. %)	OXYGEN SATURATION (MEDIAN % OF SATURATION)	OXYGEN CONCENTRATION (MEDIAN VOL. %)
Not asphyxiated	72	19.8	54.1	11
Mild asphyxia	18	18.8	44.5	9.1
Severe asphyxia	10	21	40.5	9.1

babies are either mildly or severely asphyxiated. The wide range not only of the oxygen capacity but also of the oxygen saturation shows that there are other factors with more influence on these babies at birth.

Thirteen patients were in labor when operated upon. Five babies breathed normally and were in good condition (Table V). The average oxygenation of the hemoglobin was 47.6 per cent, and this was appreciably lower than in the group not in labor. Two infants were mildly asphyxiated with an average oxygen saturation of 44.5 per cent, while 5 were severely asphyxiated with an average saturation of 40 per cent. The 2 premature twins with erythroblastosis who died in a few hours were well oxygenated at birth. Here again the range shows that while it is lower in the category of asphyxia, it is still not the most important factor in the production of this condition.

TABLE V. EFFECT OF LABOR ON THE CONDITION OF THE BABY (13 CASES)

CONDITION OF BABY	NO. OF CASES	AVERAGE OXYGEN SATURATION (%)	RANGE
Not asphyxiated	5	47.6	14.5-65.5
Mild asphyxia	2	44.5	27.9-61
Severe asphyxia	5	40	14.7-78.5
Died	1 (premature erythroblastotic twins)	73	58.9-87.1

We next studied our cases according to premedication. All mothers had atropine or scopolamine, $\frac{1}{150}$ grain, preoperatively. Fifteen mothers had 50 mg. of Demerol, and the infants had a median oxygen saturation of 54.4 per cent. Nine had 75 mg., with an oxygen saturation of 58 per cent in the infants, and 6 had 100 mg., with an oxygen saturation of 65.3 per cent in the infants.

TABLE VI. OXYGEN SATURATION OF BABIES ACCORDING TO PREMEDICATION
(All had scopolamine or atropine, 1/150 grain, preoperatively)

	NO. OF CASES	AVERAGE SATURATION (%)
Demerol 50 mg.	15	54.4
Demerol 75 mg.	9	58.0
Demerol 100 mg.	6 (7 babies)	65.3

Eliminating all patients in labor and those with hemorrhage or toxemia, we found that in 22 cases in which Demerol was given preoperatively the median oxygen saturation of the infants was 64.6 per cent, while in those without Demerol it was only 54.2 per cent. Our anesthesiologist (N. B.) has believed that any respiratory depressant drug is contraindicated. However, the pharmacology of meperidine (Demerol) gives us a valuable clue to the answer.

Drill[9] stated in his *Pharmacology in Medicine* that meperidine is chemically more closely related to atropine than to morphine. It is analgesic and mildly sedative but also possesses antispasmodic properties. In the appropriate doses it has only a slight effect on the rate and depth of respiration, while morphine has not only analgesic and sedative properties but also has a spasmogenic effect. For this reason, it has been used for years in combination with atropine. Our results bear out this pharmacological evaluation of meperidine and we now feel that selected sedation before cesarean section is not contraindicated but is desirable. Little[6] went even further and said that the mild respiratory depression of proper sedation may help prevent aspiration.

TABLE VII. OXYGEN SATURATION IN CESAREAN SECTIONS WITH NO ADDED RISK
(Premedication—atropine or scopolamine)

	NO. OF CASES	MEDIAN SATURATION (%)	MEDIAN OXYGEN CONCENTRATION (VOL. %)
Demerol, 50-100 mg.	22	64.6	13.1
No Demerol	60	54.2	10.8

Working on the supposition that Demerol (meperidine) would have no effect on the oxygen saturation at birth but might cause a fetal apnea and thus asphyxia after delivery, the condition of the babies delivered of mothers with and without Demerol was checked (Table VIII). Eliminating the 3 deaths which had no connection with the method of delivery, we found 27.1 per cent of the no-Demerol babies in some degree of asphyxia, while 30 per cent of those whose mothers received Demerol were asphyxiated. Sedation is often given during a trial of labor, however, and since labor increases the incidence of asphyxia, we eliminated the 12 infants of mothers who were in labor. The incidence of asphyxia then dropped to 13.6 per cent in the Demerol group, but remained at 27.3 per cent in the no-Demerol group.

TABLE VIII. CONDITION OF BABIES AT TIME OF BIRTH WITH AND WITHOUT DEMEROL

CONDITION OF BABY	ALL CASES		NOT IN LABOR	
	DEMEROL	NO DEMEROL	DEMEROL	NO DEMEROL
Mild asphyxia	3	15	2	14
Severe	6	4	1	4
Good	21	51	19	48
Dead	2 (erythroblastotic twins)	1 (placental separation)	0	1 (placental separation)
% in asphyxia	30	27.1	13.6	27.3

TABLE IX. CONDITION OF BABIES ACCORDING TO BLOOD PRESSURE OF MOTHERS AND ADMINISTRATION OF OXYGEN

	NO. OF CASES	GOOD	MILD ASPHYXIA	SEVERE ASPHYXIA	DIED LATER
No oxygen and no blood pressure drop	15 (16 babies)	10	3	1	2 (erythroblastotic twins)
Oxygen and no blood pressure drop	22 (23 babies)	13	5	5	0
No oxygen and blood pressure drop	13	12	1	0	0
Oxygen and blood pressure drop	50 (51 babies)	37	9	4	1 (placental separation)

The effects of the administration of oxygen and the incidence of blood pressure drop were then studied (Table IX). It appears that when a drop in blood pressure occurred and no oxygen was administered, the babies were in better condition. However, oxygen was administered to the mother in all of our complicated abdominal deliveries and a drop in blood pressure was immediately counteracted by vasopressors, so we believe that our apparent statistical results are complicated by other factors more important than a temporary condition which is quickly corrected by an alert anesthesiologist. To assure this alertness, one of the cardinal rules of our Department of Anesthesiology is that an intravenous solution of glucose or blood is started immediately after the anesthetic is given.

The condition of the babies according to birth weight was also checked (Table X). Those that weighed under 2,500 grams and over 3,500 grams, showed a definitely higher incidence of asphyxia than those in the middle group. The condition of the premature babies is understandable. Two mothers were in labor and 4 were toxic. There were 4 cases of placenta previa and one elderly primipara with a contracted pelvis. One pregnancy was complicated by a fibroid. It is surprising that, despite these complications added to prematurity, all of the babies were discharged in good condition.

TABLE X. CONDITION OF BABIES ACCORDING TO BIRTH WEIGHT

WEIGHT (GRAMS)	NO. OF CASES	GOOD	MILD ASPHYXIA	SEVERE ASPHYXIA	DIED
4,000 +	11	7	2	2	0
3,500-3,900	20	13	3	4	0
3,000-3,499	36	29	6	1	0
2,500-2,999	19	15	3	1	0
2,000-2,499	11 (12 babies)	6	4	2	0
Under 2,000	2 (4 babies)	2	0	0	2 (erythroblastotic twins)
Unknown	1	0	0	0	1 (placental separation)

The infants were also checked according to the mother's preoperative hemoglobin (Table XI). Eighteen of 47 babies with the mother's hemoglobin under 12 Gm. showed some degree of asphyxia, while only 10 of 53 with a higher hemoglobin were clinically asphyxiated at birth.

TABLE XI. CONDITION OF BABIES ACCORDING TO PREOPERATIVE MATERNAL HEMOGLOBIN

HEMOGLOBIN (GM. %)	NO. OF CASES	GOOD	MILD ASPHYXIA	SEVERE ASPHYXIA	DEAD
8.9- 9.9	3	2	0	1	
10 -10.9	15	10	3	2	
11 -11.9	30 (31 babies)	17	10	2	2 (erythroblastotic twins)
12 -12.9	17	14	1	2	1 (abruptio placentae)
13 -13.9	24	21	2	1	
14+	11 (12 babies)	8	2	2	
Under 12	47	29	13	5	2 (erythroblastotic twins)
Over 12	53	43	5	5	1 (abruptio placentae)

In the 100 cases there were 103 babies. Three of these died, but the deaths could in no way be ascribed to the procedure. Of the remaining 100 infants, 18 were mildly and 10 severely asphyxiated. Five developed clinical atelectasis confirmed by x-ray. Two cases were so severe that hyaline membrane was diagnosed but both infants recovered clinically and were normal by x-ray. All 100 babies left the hospital in good condition.

We were concerned before this study was undertaken by the incidence of asphyxia and the danger of aspiration at the time of delivery. Our method of handling these infants was established long before we started our investigation. One of us (N. B.) is head of the Department of Anesthesiology at Providence Hospital and for many years has been interested in the problem of anesthesia in cesarean section and the immediate welfare of the child. All of our patients were given 0.6 c.c. of 1 per cent Pontocaine (6 mg.) plus 1.6 c.c. of 10 per cent dextrose in the second lumbar interspace. In one case the anesthesia failed and cyclopropane was used. All patients were given 10 mg. of D-desoxyephedrine intramuscularly before the spinal anesthetic was administered. The Department head, his associate, and the anesthesiology residents gave all of the anesthetics. Blood pressure readings were frequently taken and vasopressors and oxygen were used whenever indicated. As soon as the child was born it was turned over to the anesthesiologist. The stomach was thoroughly aspirated and then, under direct vision with a laryngoscope, the trachea was aspirated, and oxygen administered. We feel that the meticulousness and speed with which this was done were very important in the recovery of these infants. Particularly important is the aspiration of the stomach because of the frequency of regurgitation and inhalation of irritating stomach contents. The reports of Sunderman and Boerner[10] indicate that stomach acidity is high on the first and second day of life. This acid, regurgitated and mixed with amniotic fluid and blood, undoubtedly precipitates protein. If aspirated, the alveoli and smaller bronchi will be coated with an albuminous deposit. This is recognized as a hyaline membrane.

When a child is born normally, its passage through a snug birth canal prevents sucking in of foreign material. Vernix, meconium, and blood are usually not available for aspiration. Even if the child gives a convulsive gasp in an effort to breathe, little or nothing is inhaled until the mouth is free of the vulva. In cesarean sections, however, and possibly more often in the low cervical than in the classical operation, it takes an appreciable length of time for the head to be extracted after the uterine incision. This time varies with the degree that the head may be wedged in the pelvis, the size of the baby, and the facility of the obstetrician. It is during this time that the baby frequently gives a gasp and, since there are blood, vernix, amniotic fluid, and occasionally meconium in the field, aspiration of these elements is much more common than during normal delivery. So it is not surprising that many cesarean babies are asphyxiated.

Comment

Our studies have proved to us that the oxygen capacity and the oxygen saturation in the newborn are not the most important factors in survival of the cesarean-born infant. Although the optimum saturation of oxygen in the arterial blood of the newborn is 60 to 65 per cent, we have found values as low as 10.2 per cent with recovery. If the respiratory tract is clear and the medullary centers are intact, the oxygenation of the blood rises rapidly as the baby begins to breathe. This has been shown by Taylor[11] and Montgomery.[12]

If the decrease in oxygenation is combined with aspiration or with a depressed respiratory center, however, it may be an important factor in the death of the infant.

We have found that premature and oversized babies show a higher percentage of asphyxia. We note that the use of Demerol before cesarean section has no apparent deleterious effect on the child and may even be beneficial.

The emergency indications for cesarean section always present a hazard to the child. The patient with separation of the placenta or placenta previa frequently has an asphyxiated baby. We have shown that the same is true if the patient has had a trial of labor, but this does not fully account for our incidence of 28 per cent of asphyxia.

For a more complete explanation of this high incidence, we must look further. Cutting through the placenta will result in fetal blood loss as has been shown by Siddall and West.[13] Difficulty in delivering the head, especially if it is low in the pelvis, gives added opportunity for aspiration. The inevitable presence of blood in the operative field introduces another hazard if respiration begins before the head is delivered. Therefore, the cesarean-born baby is particularly ripe for respiratory difficulty. Others have recognized this and it is customary in well-equipped hospitals to turn the infant over to an anesthesiologist or a competently trained pediatrician to clear the air passages. Simple aspiration of the pharynx or trachea is not sufficient because as the child aspirates he swallows and the stomach may be filled with a mixture of blood and amniotic fluid. In an effort to clear his own air passages, the infant regurgitates and the stomach contents are not infrequently sucked back into the lungs. Since there is a relatively high degree of acidity in the stomach of the newborn, the interaction of hydrochloric acid and protein may well be the cause of the development of a hyaline membrane or atelectasis in the lungs of the infant. We had 5 such cases in our series, so we believe it is important to empty the stomach first, and then aspirate the trachea.

Conclusions

1. The oxygenation of the cesarean-born infant is appreciably lower than in all others except those born by the most difficult of vaginal deliveries.

2. Due to blood pressure instability, the oxygenation of the child is slightly lower under spinal than under general anesthesia but the absence of respiratory depression in the infant with block anesthesia influenced us to choose spinal as the anesthesia of choice.

3. Interference with placental circulation, due either to placenta previa, placental separation, or to cutting through the placenta, interferes with fetal oxygenation.

4. Labor increases the incidence of asphyxia in the cesarean newborn.

5. Babies of mothers with hemoglobin under 12 Gm. showed increased asphyxia in comparison to those with readings over 12 Gm.

6. The high incidence of asphyxia in the cesarean-born infant is due, we believe, to aspiration at the time of delivery.

7. Emptying the stomach and then aspirating the trachea immediately after birth are essential parts of the immediate care of the cesarean newborn.

8. Demerol, in moderate doses, does not have a deleterious effect on the oxygen saturation of the newborn infant nor does it apparently reduce the respiratory response. In our experience, it actually decreases the incidence of asphyxia.

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Discussion

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—The authors obviously realize that while a single oxygen determination from the fetal cord at birth may indicate some pre-existing undesirable situation it does not answer certain important questions; namely: (1) What was the precise etiological factor? (2) How long had this detrimental factor been at play? (3) What pathologic changes may have taken place as a result? (4) How will the respiratory mechanism of the newborn henceforth function? (5) Will permanent damage result?

The answers to these various important questions are difficult to secure from studies in the human subject, and the results of animal experimentation are not always directly applicable.

Serial determinations of oxygen saturation of the human fetus after delivery, as introduced by Stewart Taylor, are important in determining the ultimate behavior of respiratory function in the newborn and have value from the point of view of prophylaxis and therapy. These latter determinations may be made chemically from peripheral blood, or with considerable accuracy with the direct reading oximeter.

Gross pathologic changes in the central nervous system which result from hypoxia may become manifest as infant life advances; subtle and less dramatic changes are difficult to determine by any of the present techniques. Indeed, the tolerance of the newborn to transient hypoxia has not been determined, although it is said to be considerable. In the several instances where we have followed up low serial determinations of oxygen saturation, the electroencephalographic determinations have thus far shown no alteration of wave rhythm.

In general our determinations of oxygen saturation in the newborn have accorded with those of the essayists.

There is in many cases a delay or an impairment in the respiratory function of the cesarean-section baby which accords with easily recognizable clinical observations on these babies, and which is present even in elective cesarean section.

The type of anesthesia appears to play a part in this respiratory difficulty. The results of our own serial determinations have been best where local or spinal anesthesia has been employed.

All of the workers in this field are conscious of the fact that much more needs to be investigated in the field of fetal and placental respiratory function, yet these findings of gross disturbances of oxygen saturation levels in the newborn alert the obstetrician to the ever-present danger of hypoxia in the newborn and the significance of his various techniques of anesthesia, operation, and handling of the baby.

DR. CLYDE L. RANDALL, Buffalo, N. Y.—The data reported by Dr. Henderson require careful analysis, particularly the author's consideration of the many factors affecting the oxygen measurable in fetal blood at the time of birth.

The fetal apnea apparently inherent in delivery by section needs emphasis, just as the sectioned baby's tendency to atelectasis and to regurgitation aspiration has repeatedly been emphasized in recent years.

The lowered degree of oxygen saturation in the fetus whose mother was sectioned under block anesthesia is disturbing. With an informed, alert anesthesiologist, it does not seem likely that a drop in maternal blood pressure under spinal anesthesia could largely account for the noticeably better oxygenation of fetal blood when general anesthesia is employed.

Obviously, the precise time during or following delivery at which fetal blood was collected for the determination of oxygen saturation must be taken into consideration. Unfortunately, Dr. Henderson's data do not seem specific on this important point. One set of factors might account for a lowered oxygenation of fetal blood at the time of birth, while completely different factors may determine the length of time a poor degree of oxygen saturation persists in the newborn infant's blood after the cord is severed. Babies born by section particularly would be likely to require a longer-than-average time to improve the degree of oxygen saturation measurable at the time of their birth.

Dr. Henderson has, I believe, rightfully emphasized the risks of fetal aspiration during delivery by section. His data suggest that the preoperative use of Demerol and a general anesthetic seem to decrease rather than increase the probability of babies being poorly oxygenated at birth. Similar observations have led others to believe that it is desirable to have produced by premedication or general anesthesia some degree of respiratory depression in the fetus before efforts are begun to extract it from a fluid-filled uterus.

Time does not permit speculation as to why the blood of babies born spontaneously has a significantly lower oxygen content than of those delivered by low forceps. It is evident that breech delivery, while involving universally respected risks to the fetus, does not usually depress the oxygen saturation of fetal blood to the extent likely when the fetal head—after having dilated the cervix—must next distend the pelvic floor and perineum. If maintenance of a relatively higher degree of oxygenation of fetal blood at the time of delivery proves desirable, we should not overlook the implication that spontaneous delivery, even though it offers the mother the advantages of normal childbirth, may not be the safest and best for the baby. Dr. Henderson's findings emphasize, however, that we must carefully consider the many factors which may have influenced the degree of oxygen saturation in the cases reviewed, before we alter our management of patients in an effort to maintain better oxygenation of fetal blood. Which brings us to the all-important point—just how significant, in terms of the eventual welfare of the child, are these figures indicating the relative oxygenation of fetal blood at the time of birth?

The dangers of a clinically evident oxygen want are well known. Recent studies have emphasized that it is the "nonmechanical complications of pregnancy" associated with antepartum and intrapartum bleeding and fetal anoxia, rather than the mechanical difficulties associated with delivery, that are most frequently found in the background of mental retardation, behavior disorders, epilepsy, and cerebropalsy.

At the University of Buffalo, in 1950, the Department of Pediatrics inaugurated at the Children's Hospital a long-range child growth study. Each case record began with a detailed history of the mother's health and background taken in the offices of cooperating obstetricians. Samples of fetal blood were obtained at birth by prompt clamping off of a long segment of fetal cord, in so far as possible before the child could make any respiratory effort. Electroencephalographic tracings were taken within the first hour of extrauterine life, and the rate at which oxygenation of fetal blood improved after birth was recorded by oximeter recordings. X-rays were taken of the fetal skeleton, heart size, and lung fields, and the electroencephalogram was repeated before the child was discharged from the Newborn Nursery.

In all instances the long-range, thorough character of the study was discussed with the child's parents. Cases were added to the study only when the parents expressed interest and a willingness to continue their cooperation.

Psychological testing was thorough at six months and repeated each year thereafter, together with a careful medical inquiry, complete physical examination, and another electroencephalogram. Eight hundred and fifty-nine newborn infants were accepted into the study, of which number approximately half have to date continued in the follow-up. Findings are being reported from time to time by the pediatricians in charge, and at this time several of their observations seem of noteworthy importance:

1. Development and eventual capacity and capabilities cannot be measured at birth. Even with the addition of psychological testing at 6 months, the evaluation within those first 6 months fails to recognize, among the apparently slow, duller group, which children may during their preschool years "catch up with" or surpass those whose initial ratings were noticeably superior. It is important to remember that in the majority of the group studied the differences in mental capacity suggested at 6 months seem less marked as children reach the preschool years. Dr. Henderson has noticed that babies born prematurely are likely (for several reasons) to be poorly oxygenated at birth. According to the Buffalo study, a prematurely born baby is particularly likely to have a relatively poor rating at birth and at 6 months of age and yet eventually prove to be a relatively superior child. This is important to keep in mind, for we find that if the prematurely born babies are omitted from the development study, the reported tendency of the slow or dull child to "catch up" to the average is not frequently observed.

2. To date the Buffalo study suggests that relatively few retarded children will eventually be recognized among those whose oxygen saturation at birth was above 52 per cent. On the other hand, particularly if we omit the premature, a significantly higher incidence of dull children can apparently be expected if the initial oxygen reading was below 47 volumes per cent.

We would emphasize that, while the degree of oxygen saturation at birth and the time following delivery before fetal blood reaches full saturation thus seem related to the intelligence eventually shown by the child, such a correlation is not definite enough to permit a prognosis for the individual at the time of birth. We can say, however, that there will be a significantly higher incidence of retarded or dull children among the group poorly oxygenated at birth, and relatively less chance of such handicapped children among those with a higher-than-average oxygen level at birth.

We all continue to express a willingness to question the validity of those "standard operating procedures" which seem to comprise our present-day practice of obstetrics. Perhaps too willingly we have perpetuated what we zealously have regarded as basic teachings, which we would have to admit often date back to the impressive experience of some most respected clinician.

Such observations by laboratory methods as have been reported by Dr. Henderson may well weaken our conviction regarding the advantages of spinal anesthesia for section, and shake our confidence in the traditional faith that spontaneous normal childbirth is safest and best for the child.

The measurable oxygen in fetal blood at the time of birth may not prove to be a reliable indicator of how well the delivery has preserved, or to what extent it has jeopardized, the inherent mentality of the child. It seems likely, however, that determination

of the relative oxygen saturation at birth will prove a measure by which the relative safety afforded by different types of delivery, and by different types of anesthesia, may eventually be determined. It is time that we try to define the limits of a dangerous level of oxygen want, the level below which the incidence of irreparable fetal injury begins to increase.

DR. E. STEWART TAYLOR, Denver, Colo.—I question Dr. Henderson's conclusions in regard to the importance of Demerol as a preoperative anesthetic in cesarean section. His conclusion was that it was not harmful, in fact, according to his studies, apparently beneficial. I think this is not true. Serial studies will show that, after the mother has had Demerol, the child's oxygen levels during the first few hours after delivery are depressed. The only question is whether this depression is important. I think that, if there is a normal delivery or normal elective cesarean section and a normal full-term child, with regional anesthesia the depression is not clinically important and has no relationship to the eventual adjustment of the child to life. On the other hand, as Dr. Henderson has shown in his study, there are factors present in the uterus, placental pathology, factors that occur during labor, long labor, toxemia, erythroblastosis, etc., which by their very nature compromise the respiratory adjustment and oxygenation of the child. If you add to any of these such known depressing elements as Demerol, it may be clinically important. Demerol may be "the straw that breaks the camel's back."

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—The several remarks about the determination of oxygen content in a clamped segment of cord immediately after delivery lead me to make some remarks concerning technique in these undertakings.

The clamping of a segment of cord immediately after delivery provides a very convenient material for the determination of oxygen content of the cord vein and artery at the moment of birth. It is a well-known fact, however, that when the cord circulation is abruptly interrupted following delivery there is interference with some 75 to 125 c.c. of fetal blood coming across from the placenta to the baby during the subsequent ten or fifteen minutes, particularly if the baby is kept at a lower level than the uterus and the placenta. Preservation of this continuity between the baby and the placenta may elevate the fetal hemoglobin as much as 2 Gm. over what it might otherwise be.

This additional blood may be of considerable importance to the premature baby and probably of significance in bolstering the resistance of the newborn; at least it constitutes the mechanism whereby a human animal would ordinarily and physiologically be handled after delivery.

To avoid this abrupt termination of cord circulation and still to provide representative fluid from the cord vein we have employed a sterile and properly prepared syringe and needle to aspirate the cord vein immediately upon delivery. With such a technique it is possible readily to secure 5 to 10 c.c. of blood under anaerobic conditions—an ample supply for oxygen determination either by the Van Slyke apparatus or certainly by the microgasometer.

This withdrawal of a few cubic centimeters of blood from the cord vein does not seem to interfere with the subsequent circulation to and fro through the umbilical cord. Where large series of cases of oxygen saturation determinations are being made on the newborn it appears to be of some significance to employ this technique rather than the immediate sectioning of the cord.

DR. ALFRED L. POTTER, Providence, R. I.—Dr. Montgomery has just discussed one of the measures which I was about to urge that we take to restore to the section baby certain advantages present in normal vertex delivery of which the section baby is frequently deprived. The first moments of extrauterine life are the most hazardous.

To make the transition safer the section operator should try to duplicate normal vertex birth, the safest method yet devised. In normal delivery the chest is compressed and the amniotic fluid contents of the larger air passages normally present in utero are extruded by this compression before the first breath is taken. In the attempt to duplicate this I have urged that the section operator gently compress the chest of the infant

before it inspires as he holds it head down, making use of gravity which is always working, whether the suction outfit is working or not. Then in turning the baby over to the assistant he should really turn it over, turn it over face down, so that the pharyngeal contents can run out, instead of passing it over face up, which is esthetic but insures that the infant's first inspiration will include the fluid contents of the pharynx and trachea.

By undue haste in clamping and cutting the cord the section baby is deprived of an amount of blood which the normally delivered baby derives from the placenta. The section baby may be given this placental blood by stripping the cord or by passing the intact cord and placenta, as though it were a flask of blood, along with the infant to the attendant, to allow the blood to be returned to its owner by gravity. These measures, gentle chest compression, the prone position, and the restoration to the baby of its placental blood will give the section baby more nearly normal birth conditions.

DR. RALPH A. REIS, Chicago, Ill.—The statement of the essayist that every baby born by cesarean section must have both its respiratory tract and its gastrointestinal tract intubated must be challenged. This is unnecessary instrumentation. If such a recommendation were to be followed out the country over, I am sure that the sum total of effect produced upon such babies would be much more harmful than helpful.

Starting originally with our babies born of diabetic mothers by cesarean section, we found that routine gastric lavage is completely unnecessary, particularly when the cesarean section is not done under spinal anesthesia. The average gastric content of these babies was under 5 c.c. Certainly all of us know that every baby does not require tracheal and/or laryngeal intubation and aspiration. Those that do require this will be handled much more efficiently and safely by means of the tracheal catheter.

I would make a strong plea once again for the tracheal catheter—not in the hands of the pediatrician nor anesthetist but rather in your hands and mine. Surely we obstetricians have the most continuing experience with this instrument. For this reason, it seems imperative that the newly born baby delivered by cesarean section receive immediate and continuing attention from the obstetrician who should be the most experienced in all problems concerned with resuscitation.

DR. HENDERSON (Closing).—What constitutes an asphyxiated baby is subject to as many interpretations as the number of obstetricians. We feel that we may have been strict in our classification and that others might have ignored some infants that showed only mild evidence of asphyxia.

I agree with Dr. Reis that everybody is not competent to aspirate the stomach and upper bronchi properly. However, we feel that it is a valuable procedure when properly done and our anesthesiologist trains our residents in this method. The fact that all salvageable babies left the hospital in good condition is my best argument for our attitude.

Dr. Montgomery points out that clamping the cord at once and removing the segment for blood studies deprives the child of the placental blood. This is a point well taken and I am sure our technique can be altered to include needle aspiration of the cord vessels.

We have done no late follow-up on these babies. Our problem as we viewed it was to correlate the oxygenation of the cesarean newborn with the incidence of asphyxia. We were surpised that there was not a closer relationship. Our series is large enough to help answer that question but not large enough for an adequate evaluation of the greater problem of the postnatal effects of delivery asphyxia.

Dr. Taylor thinks that Demerol is not as innocuous as our results indicate. That was our opinion also and I, personally, do not use it preoperatively. However, these are the results that we obtained. I feel that it is a point that should be pursued further.

Editorial

Results of Survey of Subscriber Opinion

Subscribers to the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY will recall that a few months ago they received a questionnaire sent to them by the Editors soliciting comment and criticism on the policies of the JOURNAL. Over 4,000 replies have been tabulated and subjected to statistical analysis and interpretation.

Those who subscribe to the JOURNAL fall into three general categories, namely, specialists in obstetrics and gynecology, 45 per cent; practitioners of medicine particularly interested in the subject, 29 per cent; institutional subscribers, including libraries, basic science departments, interns and residents, 26 per cent. With this broad subscriber pattern, it was to be expected that the questionnaire would reveal a wide range and even some conflict in interests.

The replies to the formal queries asked in the questionnaire have been analyzed in relation to the various types of subscribers, with regard to special interest as well as to geographic distribution. The details of the study are obviously beyond the scope of an editoral, but some comments on the replies of all groups taken together seem necessary. There were four subjects in which over 80 per cent of those who replied evinced special interest, namely, gynecological surgery, editorials, cancer of the reproductive tract, sterility and infertility. There were also four subjects receiving between 75 and 80 per cent of favorable replies: toxemia of pregnancy, complications of pregnancy, reviews of progress, and an immediate publications department. Five topics received between 70 and 75 per cent approval: abnormal labor, hemorrhage in pregnancy, abstracts, nutrition, and the reprinting of classical papers. The correspondence section and book reviews were approved by between 60 and 70 per cent. The fact that those who answered the questionnaire were not consistently "yes men" was indicated by a disapproval of Interlingua summaries by an impressive four-fifths of those replying. The replies received will be an invaluable guide to publishers and editors in the future.

Perhaps of even greater interest than the replies to the precise questions that had been asked were the general comments that were volunteered. These ranged from sharp criticism to strong approval and concerned all aspects of publishing and editorial policy. As extreme examples, there was one suggestion that the JOURNAL be published weekly, one request for emphasis on psychosomatic gynecology. It is impossible here to refer to more than the comments which occurred repeatedly, and to indicate the areas in which comments were made.

Journal Format.—There were suggestions that the JOURNAL be made larger and that it be made smaller, that it be printed in two columns and that it remain in single columns, that illustrations be better and more numerous. Many of the suggestions must remain for the present a subject for study, but one recurring request has already been acted upon. The table of contents, for long somewhat difficult to find on page 6, began on January 1 to appear on pages 1 and 2 immediately inside the cover.

Society Papers.—A number of comments were made on the publishing of papers read before societies, two in particular. First, it was implied that too many were accepted simply because they were society papers; second, that the delay in publication of society papers was too long. With regard to the first criticism, the Editors wish to point out that all papers submitted by societies are in fact not accepted, and, second, that every effort is being made to work with secretaries and publication committees of the various societies to discourage the submission of papers which might indeed not reflect credit on the society from which they emanate. With regard to delay in publication of society papers, it should be remembered that a part at least of the waiting period is time lost in the receipt of the papers by the publisher. For the national societies, the schedule we strive for assigns a month to the collection of papers and discussions, a month to the editorial work and four months to actual publishing. A longer delay may result if the papers are submitted late by any particular society or if papers already received in the editorial office have to be sent back to the original author for corrections or rewriting.

Research Versus Clinical Practice.—Some of the most strongly worded criticisms received tended to cancel each other out, since they obviously reflected the divergent interests of different groups of readers. The most clearly defined conflict was found in the contrast between such comments as "make it a high class research journal" and "concentrate on practical clinical articles." The Editors do not delude themselves into thinking that all articles can be of interest to all readers, nor do they believe the time has yet come to segregate investigation in obstetrics and gynecology from the practical consideration of its clinical responsibilities.

Better Selection.—The most common of all admonitions was that the Editors be more "selective" in their acceptance of articles. In some respects this comment only reflected the desire of individual readers for more articles concerned with their own particular interests. There was, however, a persistent suggestion that some articles that had appeared were simply too long, too badly written, too statistical, too repetitious, or too routine to have appeared at all. This criticism requires most serious consideration.

The point must first of all be made that the commentators have no real right to the assertion that articles are badly "selected," since they have not had the opportunity to survey the declined material. What seems really to be meant is that some articles that appeared should have been left out even at the expense of having a JOURNAL shorter perhaps by one or two articles in each issue.

Review of the records of the handling of papers in the Editors' offices shows that about 25 per cent of all submitted manuscripts are declined outright and another 30 per cent are sent back to the authors for significant revision. This represents numerically a considerable degree of "selection."

The Editors recognize their responsibility to the readers of the JOURNAL, but also a measure of it to their contributors. The beginner who is writing his first paper must not be too much discouraged, the older physician must be accorded the respect which experience has won for his opinions. To balance these considerations against the views of many of our readers that enough selection is not being applied in the acceptance of manuscripts presents to the Editors their principal problem.

Clearly all of the comments require a rethinking of the basic question of for whom and for what purposes the JOURNAL is published. Objectives will, therefore, be the subject of a second editorial to be published in the near future as a result of points raised by the questionnaire.

W. J. D.
H. C. T.

Case Reports, New Instruments and Methods

ABDOMINAL PREGNANCY SUBSEQUENT TO TOTAL HYSTERECTOMY*

A Case Report

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ABDOMINAL pregnancy per se is a relatively rare condition, which occurs only once in approximately 12,000 pregnancies. In spite of this, a voluminous literature has accumulated, with slightly over 500 reported cases in the third trimester alone. The occurrence of abdominal pregnancy following hysterectomy is so exceedingly rare that the possibility is almost inconceivable. A review of the literature discloses a total of 8 cases of pregnancy following subtotal hysterectomy. These are reported by Ziprick and Crawford,[4] Stanley-Brown and Shields,[3] Connors, Cresci, and Glass[2] and others. No case of pregnancy following total hysterectomy can be found. In the 8 reported cases, several patients menstruated following operation so it is likely that only a partial hysterectomy was done. In addition, some describe a partial muscular covering over the fetal sac. The case of Ziprick and Crawford was said to be a pregnancy contained in the lower portion of the uterus. In one case, vaginal delivery of a six months' living fetus occurred four years following a partial hysterectomy. In most of these cases the proximal end of the tube had been sutured to the cervix. In one case, both tubes and one ovary had been removed, leaving the remaining ovary adjacent to the cervical stump. The following case report is of interest not only because of its rarity but because of the pitfalls in the management of this problem.

Mrs. W. E. F., a 38-year-old white gravida iii, para iii, first presented herself on Nov. 16, 1955, having been referred by Dr. John Russell, Cleveland, Mississippi, with irregular vaginal bleeding. This had consisted primarily of spotting for the past six months with two severe episodes of bleeding. Her past history disclosed that the patient had had three children all of whom were delivered prematurely. A bicornuate uterus had been diagnosed at the time of her second pregnancy. Pelvic examination at the time of this visit showed a normal-sized uterine fundus and no adnexal masses. The cervix was large, irregular, and severely eroded. There were two old healed cervical lacerations. A

*Presented at a meeting of the Memphis Obstetrical and Gynecological Society, March 13, 1956.

cervical biopsy taken at this time was reported as showing chronic cervicitis. On Nov. 28, 1955, a total hysterectomy was done by Dr. Russell. He reported that both tubes and ovaries appeared normal and were not removed. There was no evidence of pregnancy grossly or on microscopic examination of the operative specimen.

The patient did exceedingly well postoperatively and progress was considered satisfactory until Feb. 5, 1956, at which time lower abdominal pain was noted, accompanied by distention which was attributed to gas. On Feb. 15, 1956, ten days after the onset of pelvic pain, the patient was again examined. The vaginal cuff was well healed. There was a 6 cm. mass easily palpable above the vaginal cuff but otherwise movable. Aspiration showed 5 c.c. of dark blood and clots. The patient was given analgesics and advised to return home and take hot sitz baths regularly. On February 20, the patient again returned and stated that the pain had continued, becoming somewhat worse than originally. Examination at this time showed a pelvic mass now 10 cm. in diameter and in the same position as before. Aspiration through the vaginal cuff obtained 20 c.c. of blood. The following day the pain became so intense it was necessary to admit the patient to the hospital. On February 22, an incision was made through the upper vaginal mucosa and the cul-de-sac entered. The pelvic mass was easily palpable. An incision was made into the mass, resulting in profuse, active, bright-red bleeding. Gauze was immediately packed through the culdotomy incision and immediate preparations made for laparotomy.

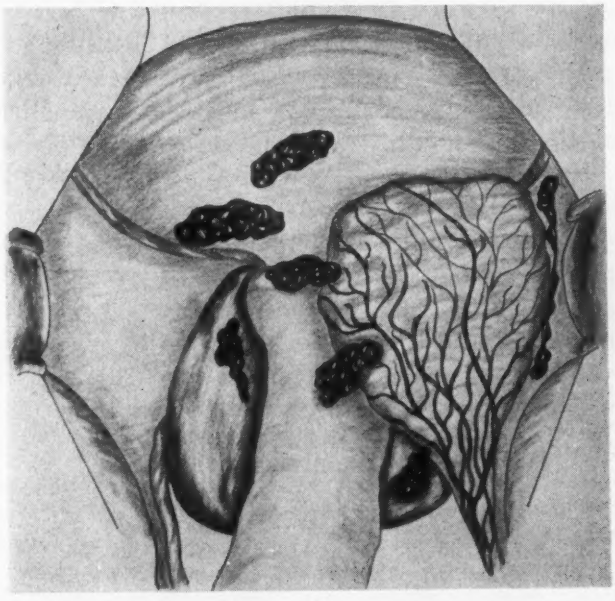

Fig. 1.—Diagrammatic drawing of abdominal pregnancy. The sigmoid is shown in the midline posteriorly and the bladder anteriorly. The placenta mass is located on the right obtaining its blood supply from the right infundibulopelvic ligament.

The abdomen contained approximately 400 to 500 c.c. of old blood and clots. The omentum was adherent to the bladder region, to the left pelvic wall, and to the pelvic mass. The sigmoid was adherent to the left pelvic wall. The blood clots were evacuated and the omentum freed from the pelvic mass which was approximately 12 to 15 cm. in diameter and extended from the right pelvic wall over to the region of the vaginal cuff. It was adherent to the right pelvic wall and appeared to be obtaining its blood supply through the right infundibulopelvic ligament. It actually appeared to be contained within the infundibulopelvic ligament. There were large dilated blood vessels coursing through the right infundibulopelvic ligament and spreading over the mass. No gross evidence of a tube or ovary could be found on either side. We were successful in freeing the mass and

in clamping its blood supply against the pelvic wall at the right infundibulopelvic ligament. During the process of removing the mass it was ruptured and large pieces of placenta immediately were apparent. There was an amniotic sac containing a 14 cm., well-developed, living fetus. With considerable difficulty hemostasis was obtained. It is customary in the management of these problems to pack when hemostasis cannot be obtained otherwise. However, this was not necessary in this case. Two rubber drains were placed in the pelvis and brought out through the vaginal cuff. The postoperative course was entirely satisfactory and the patient was discharged home on March 4, 1956.

Pathological examination of the operative specimen showed 220 grams of placental tissue mingled with a considerable amount of clots. There was a fetus which weighed 45 grams and measured crown to heel 12 cm. It was contained in a well-developed amniotic sac. Grossly no tubal or ovarian tissue could be detected. Ovarian tissue was found on microscopic examination, however. The pathological report on this specimen was "pregnancy in corpus luteum of ovary and fetus estimated age fourteen weeks."

Comment

It is unlikely that this patient became pregnant after her hysterectomy. It was learned that intercourse occurred four days prior to the hysterectomy and six weeks after the hysterectomy. This being true, it is most likely that she conceived a few days before the operation and that the fertilized ovum was in the process of passing through the Fallopian tube at the time of the hysterectomy. The hysterectomy in all probability blocked the passage of the ovum and a tubal pregnancy was created. This either ruptured or aborted through the fimbriated end, implanting on the right ovary at the site of the corpus luteum and in the region of the right infundibulopelvic ligament. With continued growth and development the mass obtained its blood supply from the right infundibulopelvic ligament. The fact that no Fallopian tube was identifiable at the time of the operation precludes the diagnosis of primary ovarian pregnancy. We do not believe that this represents actual conception following a total hysterectomy but rather conception immediately prior to the hysterectomy and a tubal pregnancy followed by an abdominal pregnancy as a direct result of the intervening surgical operation.

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MASSIVE INTRAPERITONEAL HEMORRHAGE OF OVARIAN FOLLICULAR ORIGIN DURING ANTICOAGULANT THERAPY*

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THERE is abundant evidence of the pitfalls in anticoagulant therapy. Dicumarol and heparin are generally considered to be potentially dangerous. Even small doses of Dicumarol can cause unexpected hemorrhages which may be difficult to control.[1-5] Bleeding may originate in a wide variety of sites, the most common of which are the genitourinary tract, brain, pericardium, pleura, central nervous system, heart, lungs, and abdominal viscera. We will present 2 cases of extensive hemorrhage into the peritoneal cavity occurring during anticoagulant therapy, one originating in a mature Graafian follicle, and the other in a developing corpus luteum. Since most instances of massive intraperitoneal hemorrhage from the ovary occur with pathologic lesions, the cases reported here are exceptional in that they are associated with normal ovarian activity.

Rupture of the Graafian follicle is a physiologic process usually occurring in the mid-menstrual cycle, but it becomes pathologic when intracapsular bleeding is excessive and produces rupture. More than 300 cases of intraperitoneal hemorrhage of such ovarian origin have been reported.[6]

CASE 1.—M. A., married, age 40, para iii, gravida iii, was brought to Gouverneur Hospital on July 13, 1955, after experiencing a sudden sharp pain in the lower abdomen, dizziness, and fainting. She was in shock with a blood pressure of 70/0, imperceptible pulse, and heart fibrillating at the rate of 92 per minute. The lungs were clear to percussion and auscultation; there were diffuse abdominal tenderness, marked muscle guarding, rebound tenderness, and no peristaltic sounds to auscultation. After initial treatment for shock, a history was obtainable. Her last menstrual period was on April 2, 1955. Her periods had begun at the age of 16 years and occurred every 28 days for 3 days, with occasional missed periods.

The patient stated that she had had rheumatic heart disease since the age of 10. She had been treated at another hospital for an arterial embolism in the calf of the right leg from June 7 to July 11, 1955. During that hospital stay she received a total dose of 400 mg. of Depo-heparin and 2,300 mg. of Dicumarol, averaging 50 to 75 mg. daily of the latter drug. She also received digitoxin and quinidine in an unsuccessful attempt to reestablish regular sinus rhythm. Prothrombin time estimations varied from 2 to 3½ times the control; never did the patient have hematuria. She was discharged on July 11, 1955, with a prothrombin time of 23.5 seconds and a control of 13.4 seconds. She was to continue taking Dicumarol and to have prothrombin time determinations as an outpatient. No pelvic examinations were done. The patient stated that on arrival home from the hospital she

*Presented at the Residents' Program, New York Academy of Medicine, May 22, 1956.

experienced vague abdominal pains that were momentary and not incapacitating. The next morning the pains were more intense. She began to vomit, became dizzy, and lost consciousness. The only medication taken at home was digitoxin, 0.1 mg.

Upon admission to the medical service at Gouverneur Hospital she was treated with intravenous Levophed (before blood was available for transfusion). The blood pressure rose to 100/60 and the pulse rate to 76, with a ventricular rate of 90. On pelvic examination, the cervix was posterior and closed. The uterus was anterior and minimally enlarged. A tender 10 by 12 cm. mass was palpated in the right adnexal region. Cul-de-sac aspiration showed unclotted blood. Laboratory findings on admission were: erythrocyte count 4.01 million; leukocyte count 15,500, with a differential count of 82 per cent neutrophils, 17 per cent lymphocytes, and 1 per cent monocytes; hemoglobin 12.2 Gm.; hematocrit 39 per cent. The prothrombin time according to the one-stage method of Quick was 32 seconds with a control of 13 seconds. The sedimentation rate was 23 mm. in one hour. A diagnosis of ruptured right tubal pregnancy was made and the patient prepared for operation with 50 mg. of intravenous vitamin K and 500 c.c. of whole blood in an attempt to reduce the elevated prothrombin time. After the abdomen was opened, the peritoneal cavity was found to contain approximately 1,500 c.c. of old and fresh blood with clots. A perforated 8 by 12 cm. right ovarian cyst was discovered. After aspiration of the blood and clots, all active bleeding was controlled, the right mesovarian ligament was clamped, and the ovary removed. The abdomen was closed in layers without drainage. The patient received 1,000 c.c. of blood in the operating room. Twelve hours postoperatively the prothrombin time was 13 seconds with a control of 12 seconds. Subsequent prothrombin times were all within normal limits. Three days later, the following laboratory results were obtained: serum fibrinogen 290 mg. per cent; Lee-White clotting time 6 minutes; blood platelets 294,000 per cubic millimeter. Microscopic sections of the pathologic specimen revealed a perforated corpus luteum cyst. The patient was discharged on the twelfth postoperative day following an uneventful course.

CASE 2.—H. K., a single nullipara, aged 20, was admitted to the Beth El Hospital on Sept. 25, 1950, with chief complaints of lower abdominal pain and pain in the chest for 8 hours prior to admission. Her last menstrual period was on Sept. 4, 1950. She had been treated for venous thrombosis since Sept. 21, 1950, with Depo-heparin, receiving 900 mg. as follows: 300 mg. on the first day, with 200 mg. on 3 consecutive days. Her symptoms commenced soon after the last injection on September 25. Physical examination on admission showed the blood pressure to be 96/60, pulse 120, temperature 100° F. There was a tender ecchymotic area on the right ankle, a negative Homan's sign, and tenderness in the right calf and lower abdomen. A suggestion of rebound abdominal tenderness was also present. The diagnosis of venous thrombosis and pulmonary embolism was considered. On pelvic examination a serosanguineous vaginal discharge was found to be present. The cervix was in the proper axis, firm, and closed. The uterus was anterior and normal in size. The right fornix was negative. The left fornix was tender and full, with the suggestion of a mass. There was no bulging in the cul-de-sac. A tentative diagnosis of ruptured tubal pregnancy was made. Cul-de-sac aspiration was positive for unclotted blood. She received toluidine blue intravenously prior to operation. The blood coagulation time was 23 minutes (Lee-White method). At laparotomy approximately 1,200 c.c. of blood and clots was present in the peritoneal cavity. The uterus was normal, as were both tubes and the left ovary. A small clot was present on the right ovary and on its removal there was bleeding from the ovarian surface. This area was resected and closed with a mattress suture. The patient received 1,000 c.c. of blood in the operating room.

Microscopic sections showed a ruptured follicle cyst of the ovary. The postoperative course was uneventful. Following operation the blood pressure was 120/70 and remained normal. All evidence of venous thrombosis disappeared except for a nontender indurated area along the right internal saphenous vein. The patient was discharged on Oct. 3, 1950, in good condition.

Comment

The most frequent cause of massive intraperitoneal hemorrhage of pelvic origin is ruptured tubal pregnancy. The bizarre menstrual history preceding

rupture of the tube and the similarity to other lesions defy early diagnosis and often delay operation until rupture of the tube occurs. In both cases presented, the diagnosis of ruptured tubal pregnancy was made preoperatively because of the shock syndrome and the presence of blood in the cul-de-sac.

During the expulsion of the ovum some blood may escape into the peritoneal cavity but, according to Novak,[7] there is usually no bleeding from the stigma. In the early development of the corpus luteum, proliferation is followed by the second stage of development, that of vascularization. At this point the follicle is a grossly red, cherrylike structure protruding above the surface of the ovary which may be injured by manipulation and may rupture with varying degrees of hemorrhage. A depressed coagulation time may precipitate bleeding extensive enough to produce evidence of shock from blood loss as it did in the second case.

A corpus luteum hematoma, which is a later development, may continue to bleed, become overdistended, rupture, and produce intraperitoneal hemorrhage instead of forming a corpus luteum cyst. This may occur at the end of the cycle or become evident after a few days' delay in the expected period. Although ruptured corpus luteum cysts may occur when no anticoagulant therapy is used, the diagnosis should certainly be considered when the patient is receiving such therapy. Case 1 is due to a corpus luteum cyst progressing to rupture and massive intraperitoneal hemorrhage.

Novak described in detail the various abnormalities of corpus luteum development such as hematoma, corpus luteum persistens, etc., which give a symptom complex resembling unruptured tubal pregnancy, but he made no mention of physiologic cysts progressing to rupture and producing symptoms of a ruptured tubal pregnancy.

In this report, the amount of hemorrhage was excessive, both patients being admitted in shock. Evidence suggests that this was related to the administration of anticoagulants. The early diagnosis of these accidents is difficult, and the differentiation preoperatively from ruptured tubal pregnancy is often impossible.

Summary and Conclusions

1. Two cases are reported of massive intraperitoneal hemorrhage arising from ruptured ovarian follicular structures, occurring during anticoagulant therapy.

2. The possibility of such complications should be kept in mind by both the internist and the gynecologist.

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PRIMARY PERITONEAL PREGNANCY

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PRIMARY peritoneal pregnancy is a very rare form of ectopic gestation. That it actually can occur has been doubted by many. In fact, not until the report of Studdiford[1] in 1942 did one of our foremost authorities on gynecological pathology become convinced of its actuality. In the past few years Baldwin,[3] Kroupa and Bleicher,[4] and Ahnquist and Lund[5] have all reported new and undoubted instances of this condition. They have all reviewed the previous literature, discussed the mechanism by which this abnormal nidation takes place, and defined the criteria which must be fulfilled in order to make the diagnosis. Another discussion of these aspects would be superfluous. These cases are of sufficient rarity, however, so that all instances should be recorded. This is the basis for the following report.

Case Report

The patient was a married white woman, aged 30, para i, gravida ii. Her only previous pregnancy, three years before, had resulted in a normal low forceps delivery at term. Her past medical and surgical history was negative. Her last menstrual period was on March 26, 1954, and she was first seen by her obstetrician about a month later. Pelvic examination at that time disclosed evidence suggesting early pregnancy. She made four subsequent prenatal visits and abdominal palpation showed what appeared to be a gravid uterus enlarging at a normal rate. There was no staining or any other unusual signs or symptoms. On July 30, 1954, at about seventeen weeks, the patient first complained of moderately severe localized fundal tenderness without bleeding. She was examined abdominally and no irregularity of the uterus was observed. It was supposed that the tenderness was due to the necrosis of a small fibroid, although none was palpated. The pain was adequately controlled by codeine and aspirin.

Two weeks later the pain recurred, more severe than previously, not relieved by sedation, and accompanied for the first time by minimal spotting. The patient was promptly ordered to the hospital. This was on August 16, at which time she was about twenty weeks pregnant. On admission, the patient complained of severe shoulder and chest pain, was extremely pale, and showed the obvious signs of advanced shock due to blood loss. The blood pressure was 70/20 mm. Hg, pulse 172, and respirations were shallow and painful.

Abdominal examination showed a lower abdominal mass the size of a twenty weeks' gestation, firm, tender, but not stony hard. No irregularities could be felt abdominally and the fetal heartbeat was absent. There were no contractions. The abdomen seemed only moderately distended, with generalized tenderness and rebound tenderness present. Pelvic examination showed the cervix to be soft, uneffaced, and undilated, with a minimal amount of staining noticed on the examining fingers. Following this examination the patient passed what was subsequently proved to be a large and extremely thick decidual cast. A tentative diagnosis was made of a spontaneous rupture of the uterus at twenty

†Deceased.

weeks, cause unknown, or a ruptured ovarian cyst with intra-abdominal hemorrhage. She was operated upon about half an hour after admission while a transfusion was being given.

When the abdomen was opened, about 1,500 c.c. of free blood was encountered. While this was being cleared away, a well-formed stillborn male fetus 14 cm. in length was observed to be lying within what at first appeared to be the cavity of a ruptured uterus. The placenta was firmly attached to the wall of this space. Since the patient was 30 years of age, with only one living child, repair of the uterus was momentarily considered, but then abandoned when it was realized that the degree of the rupture was too extensive. A hand was therefore inserted deep into the pelvis to locate the cervix and other landmarks preparatory to a hysterectomy. It was then that the main body of a well-formed, symmetrically enlarged uterus the size of a four to six weeks' gestation was encountered. This was delivered into the wound. The sac containing the fetus and the attached placenta was seen to arise from the posterior aspect of the right cornu of the uterus, attached by a pedicle similar to that of a sessile subserous fibroid. The right tube was lightly adherent to it but was not involved. Its abdominal ostium was occluded. The wall of the sac adjacent to the rupture was very thin, becoming thicker as the uterine attachment was approached (Fig. 1). The uterine end of the tube and the pedicle of the mass were clamped and the tube and pedunculated mass were removed. It was noted that there were two separate structures involved after this was done. One was the cornual end of the tube and the other was the compressed muscle of the uterus. There was no connection between this latter muscular stump and the endometrial cavity of the uterus proper. It had the appearance of the myometrial pedicle of a subserous fibroid. These findings were puzzling because they did not suggest the typical cornual pregnancy.

Both stumps were then sutured and the raw areas peritonized. The abdomen was closed in layers and the patient made an uneventful recovery after a second transfusion.

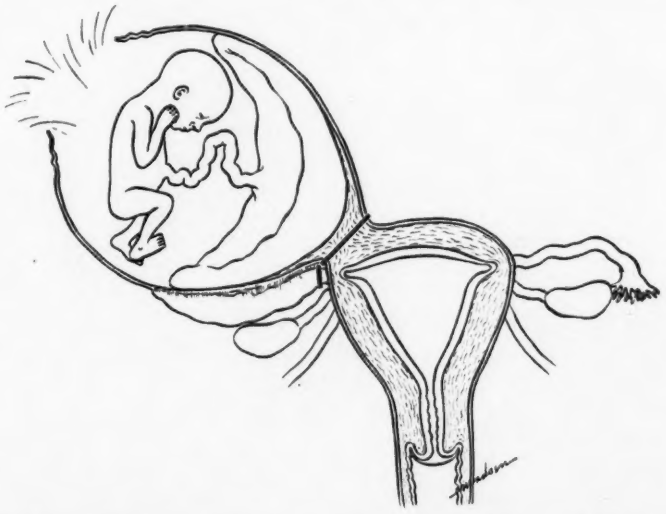

Fig. 1.—Diagrammatic representation of operative findings. Attached to the right side of the fundus uteri by a rather thick muscular pedicle is a ruptured sac. It contains a fetus and is lined with amnion; at the base of the sac is attached a well-formed placenta. The peripheral portions of the wall of the sac are clear and transparent. As the uterus is approached the walls become thicker because of an outer layer of expanded uterine muscle. The ampullary end of the right tube is intimately fused with the mass, the fimbriated extremity being occluded. The resection was carried out along the heavy lines.

Pathology Report.—(47881) Laboratory of the Doctors Hospital.

The pedunculated mass excised from the uterus had an irregular rent on the serosal side, exposing a cavity lined with an amniotic sac containing a well-formed male fetus 14 cm. in length from crown to rump. The placenta appeared normal and was firmly attached to the base of the cavity. The resected surface was soft and edematous. The

outer layer of the sac overlying the placental attachment was fairly thick and appeared to be made up of uterine muscle. As one followed the outer surface of the sac toward the point of rupture, the muscle layer thinned out and disappeared and the outer layer of the sac appeared to be amnion. The distal portion of the tube was intimately fused to the mass; the fimbria could not be identified. The isthmic segment was lightly adherent by thin fibrous strands.

The mass passed per vaginam consisted of pink-gray, soft, spongy tissue.

Fig. 2.—Placental implantation on uterine serosal surface. The chorionic villi rest directly upon the myometrium. (×30.)

Microscopy: The placenta was implanted directly upon myometrium and had normal well-formed villi. Decidual tissue was absent. The underlying muscle appeared edematous and contained a few groups of syncytial cells (Fig. 2). In the angle between the uterus and the isthmic end of the tube, a few villi lay on the serosa. Sections through the resected surface showed edematous muscle and connective tissue; endometrial tissue was absent. The isthmic end of the tube had some polymorphonuclear cells in the lumen. The wall was slightly edematous but otherwise showed nothing of note. The fimbria could not be identified; there was only fibrous tissue. Unfortunately, no sections were taken from the region where the muscle seemed to disappear and only the amniotic sac was visible grossly. There may have been a superficial layer of serosa. The mass passed prior to operation consisted of decidua.

Diagnoses: serosal myometrial implantation of placenta and decidual cast.

The pathological findings on this case did not quite fulfill the full criteria for a primary peritoneal pregnancy since the abdominal ostium of the right tube was occluded and rather densely adherent to the mass arising from the uterus. There was nothing in this patient's history, however, which suggested early rupture of an ampullar tubal pregnancy with secondary attachment to the uterus. Moreover, the relationship of the placenta to the myometrium suggested strongly that the embryonic pole of the fertilized ovum had entered the serosa of the uterus to form a blood space in the superficial myometrium. This relationship is strong enough evidence to justify considering this pregnancy as a probable example of primary peritoneal nidation of the ovum. In addition, the placenta was not related to the endometrium or to the tubal mucosa.

Summary

An unusual pregnancy of twenty weeks is reported. In spite of abnormality in one tube, the location of the placenta strongly suggests that it represents a primary peritoneal nidation on the serosa of the uterus.

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LARGE OVARIAN CYST IN A NEWBORN INFANT*

GEORGE C. FINOLA, M.D., LEONARDO QUITANGON, M.D., AND GUY V. PONTIUS, M.D., CHICAGO, ILL.

(From the Departments of Surgery, Obstetrics–Gynecology, and Pediatrics, Northwestern University and St. Luke's Hospital)

OVARIAN tumors are uncommon in pediatric practice and strikingly rare in the newborn. Costin and Kennedy[1] were able to find reports of only 200 cases of ovarian tumors in the pediatric age group. To these they added 22 cases collected over a period of 28 years at the Mayo Clinic. Of the 22, 10 were teratomas, 7 were simple cysts, 3 were cystadenomas, and there was one each of dysgerminoma and granulosa-cell tumor of the ovary. In 1951, Graves, McIlroy, and Hudson[2] stated that there were only 16 cases of ovarian tumors reported in children under one year of age. In 1942 Bulfamonte[3] reported the first successful removal of an ovarian cyst in the newborn. Since then Neikirk and Hudson,[4] Kunstadter,[5] Graves,[2] Smith,[6] and Parry[7] have described similar cases. The following case represents another such tumor successfully removed on the eleventh day of life.

Case Report

This Negro female baby was born spontaneously at term, weighing 7 pounds, 11 ounces, on Dec. 4, 1955. On the third neonatal day a mild degree of abdominal enlargement was noted. Examination of the baby disclosed a mass occupying predominantly the left lower aspect of the abdomen. The mass was circumscribed, it had slightly delineable borders, was approximately 6 to 8 cm. in diameter, soft in consistency, freely movable, and nontender. There was no concomitant constitutional or systemic derangement, particularly with reference to the functional state of the gastrointestinal and genitourinary tracts. Roentgenological studies confirmed and further evaluated the mass. A flat plate of the abdomen showed a very prominent, circumscribed, soft-tissue density on the left side corresponding to the palpable mass. Following the instillation of barium the colon was found to be normal, and the lesion appeared to be anterior to the large bowel. An intravenous pyelogram showed normally functioning kidneys without evidence of obstruction in the pelvis and ureters, or displacement of the renal shadows. Hematological and urinary findings were within normal limits. With these clinical manifestations and diagnostic findings an impression of mesenteric or urachal cyst was entertained. Differential diagnosis included: duplication of the alimentary canal, renal, neurogenic, or ovarian tumors. Exploratory laparotomy showed a dark-brown, oval-shaped, free cystic mass on a long thin pedicle which was attached to the right broad ligament. The pedicle was transfixed at the base and the tumor removed. The postoperative course was uneventful, the baby made a complete recovery and was discharged on the ninth day.

The pathological report showed a simple cyst of the ovary weighing 102 grams and measuring 8 by 6 by 4.5 cm. It had a thin wall, 1 mm. in thickness, was unilocular, and contained a cystic fluid stained brown by blood, and there were some small blood clots floating freely in the fluid.

*Presented at a meeting of the Chicago Gynecological Society, Feb. 17, 1956.

Comment

The actual cause or mechanism of cyst formation in the ovary is still uncertain but most investigators agree that the underlying basic component is the presence of some endocrine imbalance. Recent theories have generally been concerned with a suspected derangement of the gonadotropic hormone production and there is experimental evidence both in animals and humans that such a derangement can lead to the formation of cysts. Investigations of Reynolds, Delson, and Lubin[8-10] indicate that straightening of segments of normally spiraled ovarian arteries with consequent increase in hydrostatic fluid pressure into nearby follicles can create cysts. Growth and development of arterial branches and their maintenance in a spiral shape are believed to be a result of estrogen stimulation. Thus, the greater frequency of cysts in later infancy compared with the neonatal period can be explained by the disappearance of maternal estrogenic hormone from the infant's blood and consequent loss of spiral configuration of arteries. Novak states that the ovarian cysts which occur in infants are retention cysts formed by dilatation of follicles.

Fig. 1.

The most constant clinical manifestation of ovarian cyst in the newborn is the palpation of an abdominal mass, because the pedicle is long enough to permit considerable mobility of the tumor within the abdomen. Next in frequency are abdominal protuberances and signs of intestinal obstruction. In the older pediatric age group, pain is a leading symptom in all these tumors.

Pitfalls or difficulties in the diagnosis of ovarian tumors in infants lie in the fact that this unique condition is not thought of because it is so rare; that the uterus and ovaries are almost abdominal organs at this age; and because they are more abdominal than pelvic they seldom give symptoms by pressure

on the rectum or bladder. Diagnostic measures should consist of hematological and urinary studies, roentgenological evaluation of the abdomen with a flat plate, and contrast studies of the genitourinary and gastrointestinal tracts. Differential diagnosis must include such conditions as omental, mesenteric, and urachal cysts, renal and neurogenic tumors, duplication of the bowel, and intestinal obstruction.

Treatment of ovarian tumors is mandatorily surgical. The best time for operation is preferably as soon as the diagnosis is suspected, for the following reasons: newborn infants tolerate surgical procedures remarkably well during the first few days of life; waiting is usually of little material gain for the patient; operation diminishes the incidence of emergency procedures for a twisted ovarian pedicle; it eliminates the danger of rupture and peritonitis which may cause a decline in the surgical integrity of the infant; and finally, procrastination increases the likelihood of malignant degeneration. Kunstadter[5] states that whether or not an accurate diagnosis is established the presence of a persistent abdominal mass in the newborn period calls for early surgical exploration to exclude a malignant process. Energetic cooperation of pediatrician and surgeon is of paramount importance in the management of this condition.

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Correspondence

Postmortem Cesarean Section

To the Editors:

I do not feel that Drs. Kelly and Winston have accurately presented our attitude in relation to the apparent futility of postmortem cesarean section in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Vol. 72, No. 1, p. 203, July, 1956. We prefer to be actively optimistic rather than hopefully pessimistic in relation to fetal salvage in this delicate situation. A quote from our article in *Postgraduate Medicine,* Vol. 14, No. 4, 1953, entitled "Spontaneous Cerebral Hemorrhage of Congenital Origin in Pregnancy," will elucidate this point:

"The term 'extrinsic' is used to delineate these sections from those of purely, or intrinsic, obstetric origin. A cesarean section of extrinsic indication in a mother approaching a moribund state is laudatory when it is realized that such a procedure also benefits the maternal partnership. . . .

"It is admitted that such procedures are not helpful to cesarean section statistics and that to determine the proper time to intervene requires care and judgment, the lack of which could easily lead to abuse. It will also help to perpetuate the canard that it is possible to sacrifice the life of the mother in the interest of the child.

"The attempt to salvage the life of a baby after the death of its mother is salutary in design, but this highly dramatic situation is paralleled only by the futility of the histrionics involved. The gradual death of the maternal organism is followed so closely by irreversible changes to and the morbid decline of the unborn child that in all medical literature there have been reported less than 100 successful postmortem sections. Therefore it is only rational to perform a section of extrinsic indication in the presence of a lethal maternal state *before* and not *after* the inevitable deteriorating maternal condition has produced an overwhelming condition of fetal anoxia or one sufficient to jeopardize the right of the unborn to life."

The major point of difference in our approach is not one of optimism or pessimism but rather that we advocate the use of an antemortem section in a moribund patient at the first sign of fetal embarrassment: "One hour after cessation of respiration the patient's condition began to deteriorate further, with increasing cyanosis and a thready, rapid pulse. The fetal heart rate, which until this time had been around 120, dropped precipitously to 100. With the patient in bed and without anesthesia, a classic cesarean section was performed and a live male infant, in good condition with spontaneous respirations, was delivered without event." In contrast, the good results reported by Drs. Kelly and Winston produced two living but "depressed" infants at birth and subject to the hazards of cerebral anoxia upon survival.

CHARLES LEAVITT SULLIVAN, M.D.
St. Elizabeth's Hospital
Boston, Massachusetts

Aug. 15, 1956

Reply by Drs. Winston and Kelly

To the Editors:

Dr. Sullivan's comments were apparently misinterpreted by us as indicating a pessimistic attitude toward postmortem cesarean section. We are glad that this is not so and regret having misstated his position.

We would like to emphasize that the lack of enthusiasm for this procedure stems from the poor results which previous generations achieved with it. The position that this operation should occupy can be evaluated only after the vast improvements in both the resuscitation of the newborn and the care of the premature infant are taken into consideration. These very significant changes will undoubtedly influence the survival statistics of infants delivered by postmortem cesarean section.

Two other points should be emphasized:

1. The necessity of maintaining maximal oxygenation of the moribund mother, and

2. The necessity of making a diagnosis of death *immediately* on the cessation of the maternal heartbeat.

This latter can be accomplished only by continuous auscultation of the heart during the agonal phase.

HERBERT G. WINSTON, M.D.
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Albert Einstein College of Medicine
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JOHN V. KELLY, M.D.
Department of Obstetrics and Gynecology
U. C. L. A. College of Medicine
Los Angeles, California

Nov. 8, 1956

Prevention of Premature Delivery

To the Editors:

I have been making sterile vaginal examinations of all obstetrical patients at every office visit and as a routine during labor for the past nine years. It became evident very early in the study that premature delivery was always preceded by an extended period of preparation on the part of the cervix and lower uterine segment, similar to the changes which take place before normal full-term deliveries. An estimation of the state of the cervix at each examination was recorded. A notation of 0-0-4 means that the cervical canal was closed normally at the external os and also at the internal os and the cervix was 4 cm. in thickness; 2-1-3 would mean the external os was dilated 2 cm. in diameter, the internal os 1 cm., and the cervix was 3 cm. in thickness. I found that premature delivery could be predicted and an estimation made of when labor could be expected to start, by the cervical changes.

When it became evident that a patient was beginning to have cervical effacement two or three months before such changes might be expected, various methods of treatment were tried. Thyroid and antibiotics, if given well in advance, seemed to help prevent premature labor, but offered no help should labor be actually starting or imminently threatening. Then I tried various antispasmodics. I noted that N-ethyl-3-piperidyldiphenylacetate hydrochloride (Dactil*) in dosages of 50 to 100 mg. four times daily was effective in preventing the onset of labor in cases where there was thinning and/or dilatation of the cervix. Dactil seems to diminish spasms of the uterine muscle if the patient has not reached the point of actual labor. Dibutoline sulfate (Dibuline†) in dosages of 25 to 50 mg. hypodermically seems to have a more definite blocking action on uterine contractions and has been used successfully to stop more violent contractions even after clinical evidence indicated that the patient was actually in labor.

Dibuline has an atropine-like action on the eyes, with some blurring of vision, and a marked drying effect in the mouth. It produces such a marked blocking action that repeated

*Lakeside Laboratories, Inc. Dactil is available in 50 mg. capsules.

†Merck Sharpe and Dohme Laboratories. Dibuline is available only in the injectable form in 5 c.c. multiple dose vials containing 25 mg. per cubic centimeter.

use to keep labor in abeyance sometimes produces some constipation and even bladder atony. The patient tends to accept the side effects without complaint, however, when it is realized that the medication can be a means of preventing premature delivery.

Over 40 patients have been treated with these two drugs with the delivery of several babies that might otherwise have been too premature to survive.

CASE OF R. R.

Aged 20 years, gravida i, para 0; last menstrual period Nov. 7, 1954, estimated date of confinement Aug. 14, 1955.

WEEKS' GESTATION	DIAMETER OF CERVIX		THICKNESS OF CERVIX	SYMPTOMS, SIGNS, MEDICATIONS, AND TREATMENTS
	EXT. OS.	INT. OS.		
4	0	0	4 cm.	Slight vaginal spotting. Thyroid, grains iv. Progesterone, mg. 10 vaginally, b.i.d.
6				Slight brownish spotting.
16	1	0	4 cm.	Mild pain and tenderness, right parametrium.
17	1	0	4 cm.	Still moderate pain and tenderness, right parametrium. ℞: penicillin, 800,000 units, streptomycin, 1 Gm., daily for 5 days as outpatient.
21	1	0	3.5 cm.	Feeling low pressure.
26	2	2	2 cm.	Slight edema. ℞: bed rest at home; Dactil, 50 mg. q.i.d.
29	2.5	2.5	1.5 cm.	Continue Dactil and bed rest.
31	4	4	0.5 cm.	Cephalic at +1 station. ℞: continue bed rest, increase Dactil to 100 mg. q.i.d.
32	Patient hospitalized at 8:30 P.M., June 18, 1955, in mild labor. Diameter of external os, 5 cm.; internal os, 5 cm.; thickness of cervix, 0.25 cm. Cephalic presentation at +1 station. Contractions every 5 minutes, lasting 30 seconds. ℞: Dibuline, 62.5 mg. (by hypodermic); Dactil, 150 mg., q.i.d. Within 10 minutes the pains had stopped and the patient was asleep. June 19, 3 A.M.: Awake with mild, irregular contractions, Dibuline, 62.5 mg. (by hypodermic), repeated. 7 A.M.: Contractions every 10 minutes. Dibuline, 62.5 mg., repeated. Contractions stopped. 12:10 P.M.: Occasional mild contractions only. Continued Dactil, mg. 100, q.i.d. June 21: Discharged to bed rest at home. To continue Dactil and use Dibuline administered by husband, if needed.			
33	5.5	5.5	Very thin	Cephalic presentation at +1 station. Occasional contractions. ℞: continued bed rest; Dibuline, 50 mg., Dactil 100 mg., q.i.d.
36 (7/14/55)	6	6	Paper thin	Cephalic presentation at 2+ station. Has required low enema daily for one week.

Labor was induced on July 15, 1955, because of extreme constipation. After 3 hours of very mild labor, the patient was delivered of a 6 pound, 8 ounce, normal, healthy child. The postpartum course was normal.

MOSCOW, IDAHO
Dec. 22, 1956.

LARELE J. STEPHENS, M.D.

Item

American Board of Obstetrics and Gynecology

The next scheduled Examinations (Part II), oral and clinical for all candidates, will be conducted at the Edgewater Beach Hotel, Chicago, Ill., by the entire Board from May 16 through 25. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I examinations will be notified of their eligibility for the Part II examinations as soon as possible.

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Schneeberg and co-workers obtained[2] similar results. "Methallenestril (Vallestril) . . . induced satisfactory therapeutic results in 50 of 52 women with the menopause. . . . Methallenestril compared favorably with several other estrogens used in the treatment of the menopause and was free of untoward effects."

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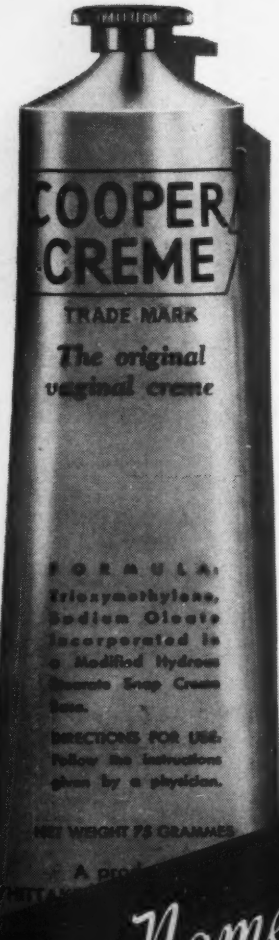

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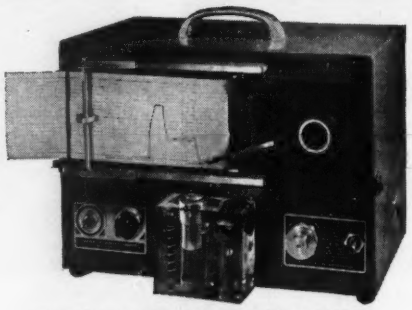

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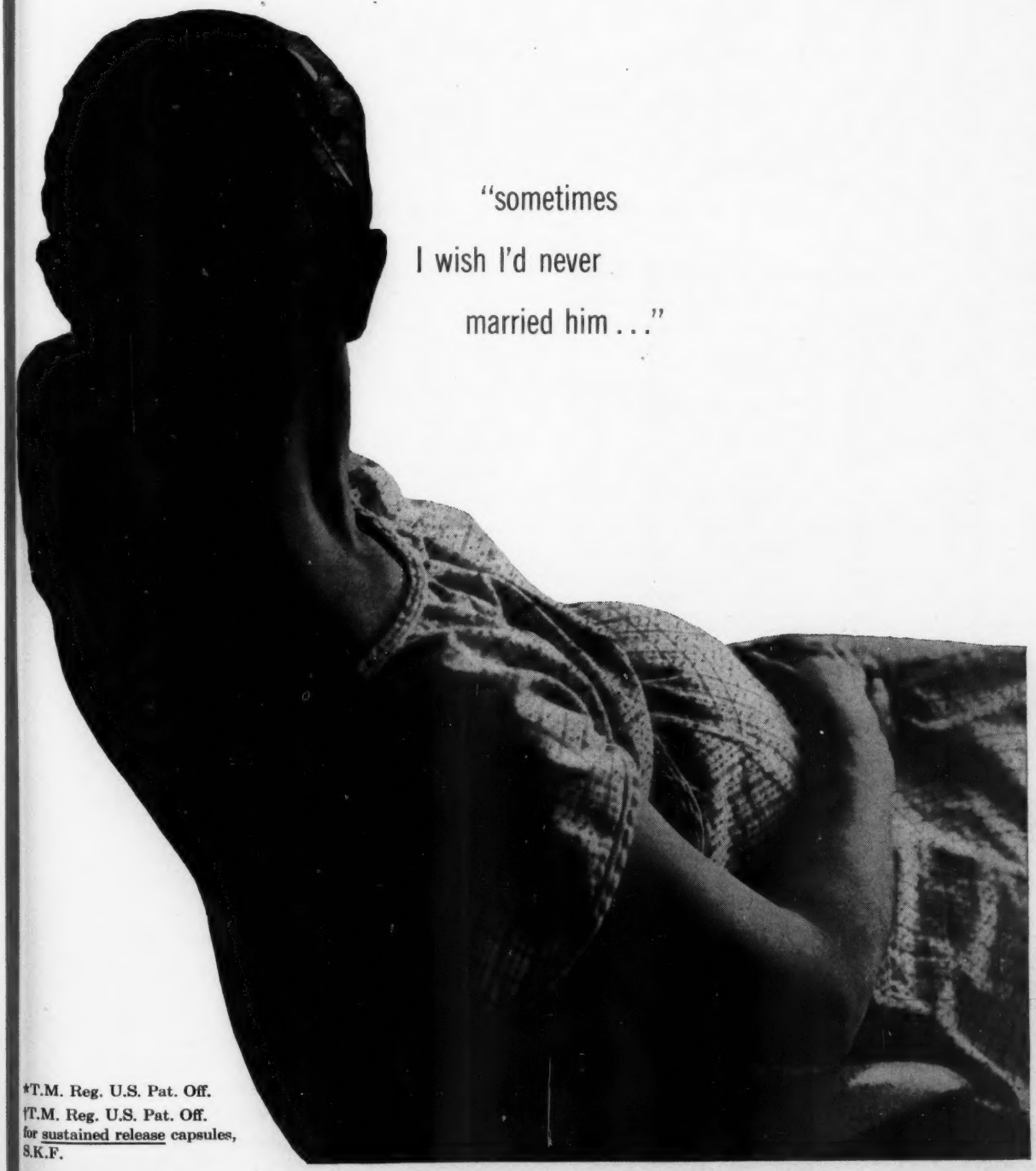

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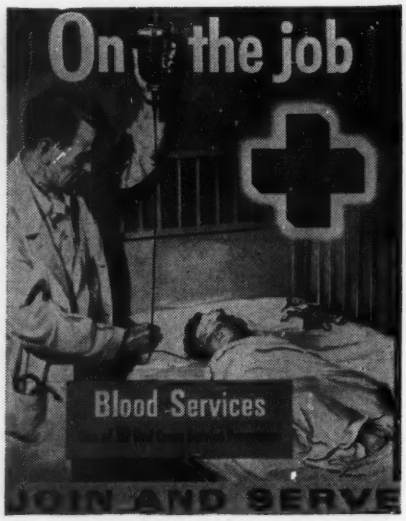

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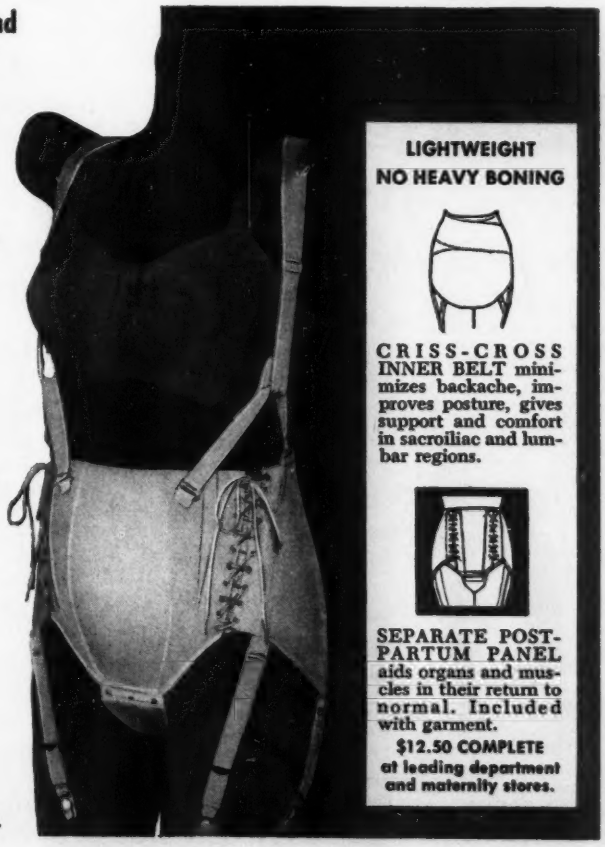
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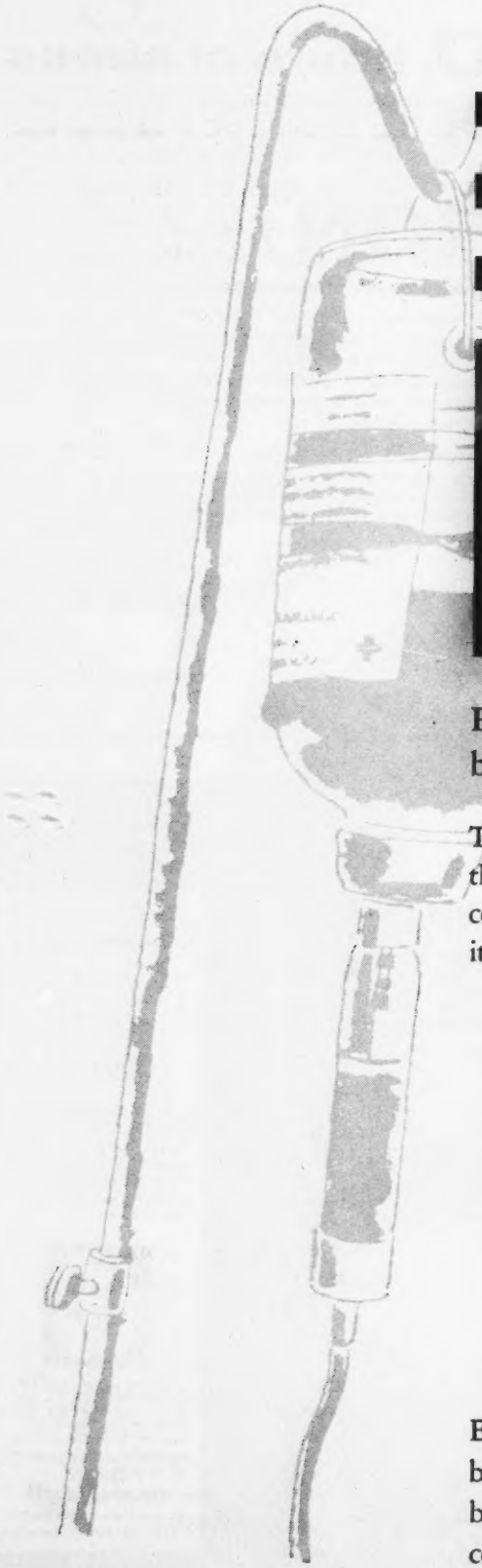

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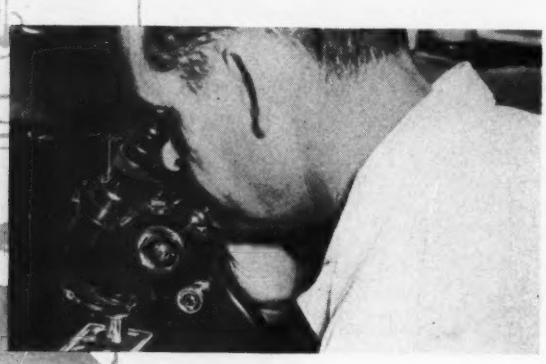

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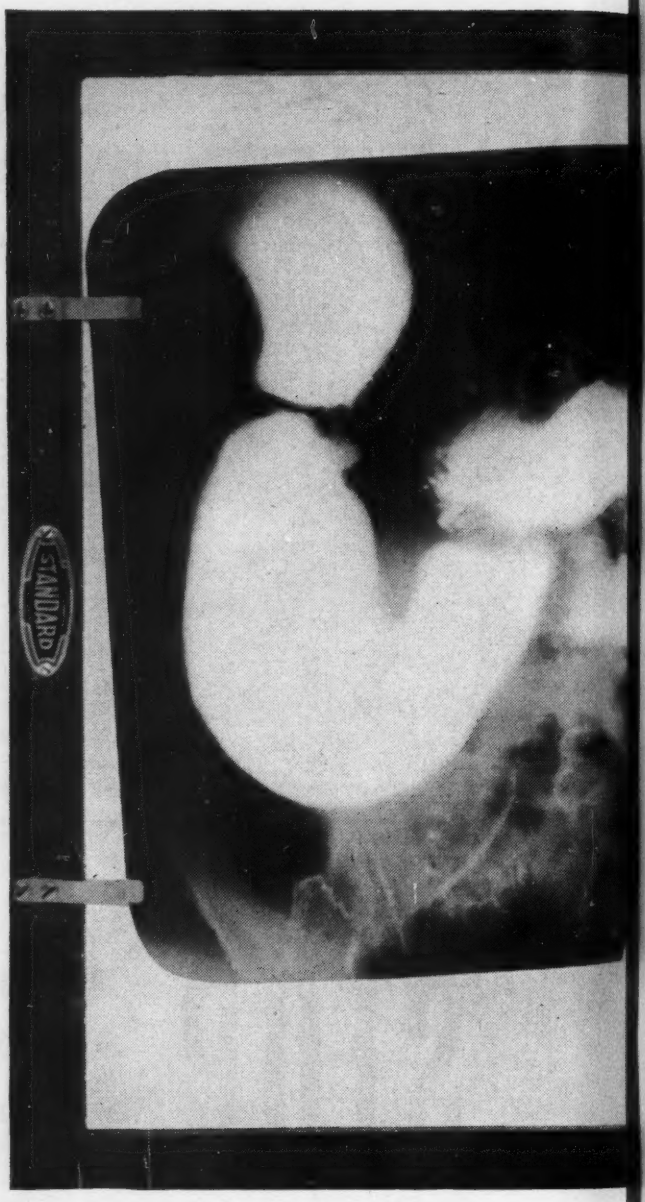

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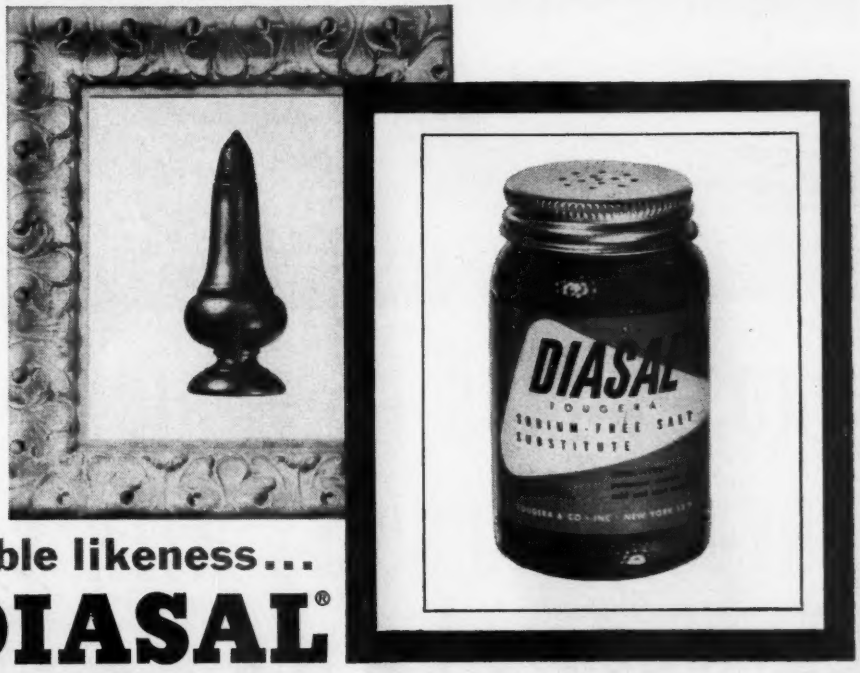

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